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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Environmental Criteria and Assessment Office (MD-52)
Research Triangle Park, North Carolina 27711

DATE: November 30, 1983

SUBJECT: Corrigenda for the First External Review Draft of 1983 Revised EPA Criteria Document, Air Quality Criteria for Lead

FROM: Lester D. Grant, Director
ECAO/RTP, U.S. EPA (MD-52)

TO: Recipients of the subject first external review draft of the 1983 revised EPA Lead Criteria Document

Copies of the first External Review Draft for the EPA Document Air Quality Criteria for Lead were recently made available for a ninety-day public comment period (October 15, 1983 - January 15, 1983), as announced in the Federal Register.

The External Review Draft of the Lead Document circulated to you and other recipients did not contain Appendix 12-C, a detailed report of the Expert Committee on Pediatric Neurobehavioral Evaluations (which was convened by ECAO/RTP to provide in-depth evaluations of studies of associations between low-level lead exposure and neuropsychologic deficits in children reported by Drs. Ernhart, Needleman, and their respective colleagues). Copies of Appendix 12-C were withheld pending reconvening of the "Neurobehavioral Evaluations" Committee in order to consider comments by Drs. Ernhart and Needleman on a preliminary draft of the Committee's report and in order for the Committee to take into account newly available published and unpublished information pertaining to the subject studies in carrying out final revision of their report. A copy of the Committee's final report is enclosed for insertion as Appendix 12-C following other Chapter 12 materials in the External Review Draft of the Lead Document recently provided to you.

Another committee was convened by ECAO/RTP in late September to evaluate certain German studies (by Drs. Kirchgessner and Reichlmayr-Lais) reporting evidence interpreted by those investigators as being indicative of beneficial effects of lead at very low exposure levels. The "Essentiality" Committee has recently completed their report evaluating the subject studies, and the report is enclosed herein. That report constitutes Appendix 12-A and is to replace the existing critique of the subject studies, which appeared as Appendix 12-A in the recently circulated External Review Draft of the Lead Document.

In addition to the above appendices, a corrigenda is also enclosed which lists corrections/notations for text and tables in the circulated four volumes of the subject draft Lead Criteria Document. The corrections noted are restricted to those thought to be crucial for accuracy or understanding of the information presented and to indicate changes apropos to the insertion of the above new appendices. Minor typographical errors or editorial changes are generally not included. There are no changes indicated to be made for Chapters 2-6 or 8 for the document.

We apologize for the unfortunate delay in our being able to circulate the above Appendix materials (for both Appendix 12-A and 12-C) to you. We also recognize the importance of their contents in terms of their crucial utility in helping to resolve certain key issues of much relevance for the development of criteria and standards for lead. In view of our delay in circulating these important materials, we are currently processing a Federal Register notice announcing a one-month extension of the Public Comment Period for that draft document to February 15, 1984. We do not anticipate any problems in having that extension and its announcement approved in time for publication in the Federal Register during the first or second week of December, 1983. We hope that this information will assist in your planning of work efforts connected with preparation of public comments.

First External Review Draft for EPA
Lead Criteria Document (1983): Corrigenda

Chapter 1

Page	Line	Correction/Notation
1-35	Table 1-4 footnote.	References cited in Table 1-4, but not provided in Section 1.14 (reference list for Chapter 1), are available in the cited Nriagu (1978b) paper.
1-36	6-7 up*	Delete "..., due complex" from end of sentence.
1-37	9 up	Replace "...mg/g..." with "...µg/g..."
1-42	13 up	Change to read: "...lead contribute differently to each of these dietary groups (Figure 1-1)."
1-48	2 up	Change to read: "...1971 Annual Report of the United Kingdom..."
1-50	1	Replace "...Association..." with "...Organization..."
1-52	23-24	Change to read: "...about 100 µg of lead is consumed daily by each American. For all Americans, this amounts to only 8 tons/year, or 0.001-0.01 percent of the total environmental contamination."
1-57	7 up	Change "...(Nriagu, 1978)" to read: "...(Nriagu, 1978a)"
1-65	1 up	Change "...(Nriagu, 1978)" to read: "...(Nriagu, 1978a)"
1-66	3,7,14 up	Change "mg" to "µg"
1-69	20	Change "primary" to "non-circumpulpal"
1-98	18	Change "1000 µg/dl" to "1000 µg/g"
1-116	2 up 1 up	Change "human" to "pediatric" Change "human studies" to "studies of children"
1-141	Table 1-20	Downward arrow should be inserted below "Vitamin D metabolism interference" entry, indicating that the vitamin D effect occurs down to 10-15 µg/dl blood lead.
1-52	12 up	"maxim safe level" should read "maximum safe level"

*Number of lines up from bottom of page (other entries are for number of lines from top of page).

Lead Document Corrigenda (continued)

Chapter 7

Page	Line	Correction/Notation
7-63	4	Change mm^3 to m^3
7-64	21	Change μ/m^3 to $\mu g/m^3$
7-69	1-2 up	Change last sentence of page to read: "For all Americans, this amounts to only 8 tons/year or 0.001-0.01 percent of the total environmental contamination."

Chapter 9

Page	Line	Correction/Notation
9-12	8	Change "secondary (circumpulpal)" to "circumpulpal"

Chapter 10

Page	Line	Correction/Notation
10-5	13 up	Change "often" to "after"
10-15	12	Line should read: "difficult to measure, and reliable values have become available only recently (see Chapter 9)."
10-20	19	Add "Shapiro et al., 1978" after "Winneke et al. 1981"
10-42	3-7 up	Sentence should read: "In a related study (Grant et al., 1980), rats were exposed to lead in utero, through weaning, and up to 9 months of age at the dosing range used in the Kimmel et al. study (0.5 to 250 ppm in the dams' drinking water until weaning of pups; then the same levels in the weanlings' drinking water). These animals showed a blood lead range of 5 to 67 µg/dl."
10-45	23	Line should read: "remains the one readily accessible measure that can demonstrate in a relative way the relationship of various effects to increase in exposure."

Chapter 11

Page	Line	Correction/Notation
11-104	17	Change "statistical relationship" to "significant relationship"
11-110	2 and 6 up	Change "per mg/g" to "per 1000 µg/g"

Chapter 11 (continued)

Page	Line	Correction/Notation
11-142	Table 11-59	Numerical table entries are in µg/dl units.
11D-23	Appendix D3	Insert revised Appendix D3 (attached single sheet) in place of comparable page in Appendix 11-D.

Chapter 12

Page	Line	Correction/Notation
12-1	19-23	Replace last two sentences of second paragraph with: "An evaluation of these studies by an expert committee convened by EPA in September, 1983, is contained in Appendix 12-A. The committee's report notes methodological problems with the studies, which preclude acceptance of the reported findings as demonstrating the essentiality of lead. These studies are, therefore, not considered further in the present document.
12-48	11 11-12 up	Change "(10 to 20)" to "(10 of 20)." Change "Reports of low blood levels..." to read "Reports of effects at low blood levels..."
12-60	4	Change "...history of pica, as well..." to read "...history of pica for paint and plaster, as well as..."
12-62	18-on	Replace the entire last paragraph of page 12-62 with: "The Perino and Ernhart (1974) and Ernhart et al. (1981) studies were evaluated by an expert committee convened by EPA in March, 1983. The committee's report (see Appendix 12-C) notes methodological problems which preclude acceptance of the analyses and findings published by Perino and Ernhart (1974) and Ernhart et al. (1981). The committee's report, further, recommends that the Ernhart data set be reanalyzed, including longitudinal analyses of data for subjects evaluated in both the Perino and Ernhart (1974) and Ernhart et al. (1981) studies. Pending resolution of methodological problems with the Ernhart data set and/or publication of adequate reanalyses, the subject studies are not considered further in this document."
12-64	5	Change "primary" to "non-circumpulpal"
12-65	7-on	After the first sentence ending with "...(see Appendix 12-C)," replace the rest of the paragraph with the following: "The committee's report notes methodological problems which preclude acceptance of the published analyses and findings reported either (1) by Needleman et al. (1979) or (2) in subsequent papers by Needleman

Chapter 12 (continued)

Page	Line	Correction/Notation
12-65	7-on	and coworkers concerning additional analyses of the same data set. The committee's report also recommends that the Needleman data set be reanalyzed. Pending resolution of methodological problems with the Needleman data set and/or publication of adequate re-analyses, the subject studies are not considered further in this document."
12-67	16 up	Change "-0.06" to "+0.06"
12-69	1 up	Add the following sentence: "The Landrigan et al. (1975) and McNeil and Ptasnick (1975) studies are, therefore, not considered further in this document."
12-83	Table 12-3	For Overmann (1977), Pb concentration should read: "5, 15, or 45 mg/kg." For Winneke et al. (1977), Pb concentration should read: "745 mg/kg (diet)."
12-84	Table 12-3	For Dietz et al. (1978), Pb concentration should read: "0.025%." For Cory-Schlecta and Thompson (1979), Pb concentration should read: "(1)0.0025, (2)0.015, or (3)0.05%." For Cory-Schelacta et al. (1981), Pb concentration should read: "(1)0.005 or (2)0.015%."
12-87	Table 12-3	For Milar et al. (1981), Pb concentration should read: "mg/kg b.w. (gavage)." For Nation et al. (1982), Pb concentration should read: "mg/kg b.w." For Winneke et al. (1982), Pb concentration should read: "0.08, 0.025, or 0.075%."
12-88	Table 12-3	Under Abbreviations, add: "b.w. body weight"
12-90	Table 12-4	For Rice and Willes (1979), Pb concentration should read: "µg/kg b.w." Under abbreviations, add: "b.w. body weight"
12-91	5 9	Change "or to "of" Change "change level" to "chance level"
12-101	Table 12-5	Under exposure protocol, the 3rd entry should end with "PND 20" rather than "PNDO"
12-115	3 5	Change "human" to "pediatric" Change "human studies" to "studies of children"
12-125	5	The 4th sentence of paragraph should read: "Proteinuria occurred in two patients."
12-216	1	Change "as much as" to "inasmuch as"

Chapter 12 (continued)

Page	Line	Correction/Notation
12-229	7 8	Change "human" to "pediatric" Change "human studies" to "studies of children"
12A-1	Appendix 12-A	Replace Appendix 12-A (pp. 12A-1 to 12A-7) with enclosed copy of "Essentiality" Committee's report labeled as Appendix 12-A.
12C-1	Appendix 12-C	Insert enclosed copy of "Neurobehavioral Evaluations" Committee's report labeled as Appendix 12-C.

Chapter 13

Page	Line	Correction/Notation
13-2	4 up	Delete "which" from line
13-22	5	Change "...about 2, may represent..." to "...about 2 µg/dl per 1000 µg/g may represent..."
13-24	Table 13-6	Entries for PbB values are in µg/dl units
13-25	Table 13-7	Entries for PbB values are in µg/dl units
13-26	Table 13-8	Entries for PbB values are in µg/dl units
13-32	Table 13-10	Under first column, "10" should be "10 µg/dl." Under last column, a downward arrow should be added immediately below the "Vitamin D metabolism interference" entry, to indicate that the vitamin D effect occurs down to 10-15 µg/dl blood lead.
13-44	12	In line 7 of the second conclusion, change "...lead contribution can be..." to read "...lead contribution to human blood lead levels can be..."
	1-2 up	Change "maxim safe level" to "maximum safe level"

Appendix D3

List of Attendees at March 10-11 and March 30-31, 1983
meeting of
NHANES II TIME TREND ANALYSIS REVIEW GROUP

Committee Members

Joan Rosenblatt (Chairman)
National Bureau of Standards

J. Richard Landis
University of Michigan

Roderick Little
Bureau of the Census

Richard Royall
John Hopkins University

Harry Smith, Jr.
Mt. Sinai School of Medicine

Invited Discussants

Joel Schwartz
U.S. EPA

J. Lee Annest
NCHS

Jean Roberts*
NCHS

James Pirkle
CDC

Vernon Houk†
CDC

Ben Forte
Ethyl Corporation

Chuck Pfieffer
DuPont

Ron Snee
DuPont

Asa Janney
ICF

EPA Staff

David Weil (Meeting Co-ordinator)
U.S. EPA

Dennis Kotchmar*
U.S. EPA

Vic Hasselblad
U.S. EPA

Allen Marcus
U.S. EPA

Observers

Earl Bryant*
NCHS

Trena Ezzote*
NCHS

Mary Kovar*
NCHS

Bob Casady*
NCHS

Robert Murphy
NCHS

Jack Pierrard*
DuPont

Kathryn Mahaffey*
FDA

*attended March 10-11 meeting only.
†attended March 30-31 meeting only.

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EPA-600/8-83-028A

INDEPENDENT PEER REVIEW OF SELECTED STUDIES BY DRS. KIRCHGESSNER AND REICHLMAYR-LAIS CONCERNING THE POSSIBLE NUTRITIONAL ESSENTIALITY OF LEAD:

Official Report of Findings and Recommendations of an Interdisciplinary Expert Review Committee

Presented by

Expert Committee on Trace Metal Essentiality

to

Dr. Lester D. Grant, Director
Environmental Criteria and Assessment Office
United States Environmental Protection Agency
Research Triangle Park, North Carolina

November, 1983

The materials contained in this report were generated as the result of critical evaluations and deliberations by the members (listed below) of the Expert Committee on Trace Metal Essentiality. All members concur with and endorse the findings and recommendations contained in the present report as representing the collective sense of the Committee.

Dr. F. William Sunderman, Jr. (Chairman)
Professor, Departments of Laboratory Medicine and Pharmacology
University of Connecticut School of Medicine
Farmington, CT 06232

Dr. M. R. Spivey Fox
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Dr. Walter Mertz
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Dr. Ekhard Ziegler
Professor, Department of Pediatrics
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TABLE OF CONTENTS

PREFACE

The Expert Committee on Trace Metal Essentiality was appointed in August, 1983 by the Environmental Criteria and Assessment Office (ECAO) of EPA, to evaluate the studies of Drs. M. Kirchgessner and A. M. Reichlmayr-Lais on the possible nutritional essentiality of lead. The Committee was provided with all relevant papers by the authors, the critiques of these papers prepared by Dr. Paul Mushak in his capacity as a consulting author of the revised Air Quality Criteria Document for Lead, and all correspondence between ECAO and Drs. Kirchgessner and Reichlmayr-Lais. Attachment 1 contains a complete list of the materials reviewed by the Committee.

The Committee convened on September 29, 1983 at the ECAO facilities in Research Triangle Park, NC. Present at the meeting were all but one member of the Committee (K.M.), Drs. Anna Reichlmayr-Lais and E. Grassmann (substituting for Professor Kirchgessner), Dr. Mushak, EPA staff, and observers from various interest groups. A complete list of attendees may be found in Attachment 2.

Following a presentation by Dr. Reichlmayr-Lais, in which she reviewed her published data as well as experiments in progress, all meeting attendees were given an opportunity to address the Committee. The Committee then pursued specific lines of questioning to its satisfaction and retired to executive session to draft its final report.

The Committee was charged with critically evaluating the studies of Kirchgessner and Reichlmayr-Lais and determining whether or not they supported the concept of a nutritional essentiality of lead. Their findings and recommendations are contained in this consensus report; views expressed by the members of the Committee in this report are their own and are not necessarily those of the institutions with which they are affiliated.

INTRODUCTION

The Committee commends Drs. Kirchgessner and Reichlmayr-Lais for their pioneering work, which is at the frontier of current research on trace metal nutrition, and wishes to express their appreciation to them for their cooperation in the Committee's efforts to assess their findings.

CRITICAL COMMENTS

The Reichlmayr-Lais and Kirchgessner data that were available for review were derived from two experiments. Based upon the published and oral descriptions of the experiments, members of the Committee expressed reservations about specific facets of experimental design, execution, and documentation, including the following:

(1) No selenium or chromium was added to the basal diet, nor were the concentrations of selenium or chromium measured in the diet to indicate nutritional adequacy of those essential elements. (In discussion, Dr. Reichlmayr-Lais indicated that Se, Cr, and other essential elements are being added to the diets in two experiments that are currently in progress.)

(2) The sole source of fat in the basal diet was coconut oil, which might render the rats deficient in essential fatty acids. (In discussion, Dr. Reichlmayr-Lais indicated that linoleic acid is being added to the diets in the experiments that are in progress.)

(3) The possibility exists that chelant residues (EDTA and APDC) may persist in the basal diet despite the extensive extraction procedures that were employed. Documentation of the EDTA or APDC concentrations was lacking and the Committee considered that HPLC or radiotracer experiments would be advisable in order to address these concerns.

(4) As the basal diet was prepared, iron supplements were added in an aqueous mixture with several other inorganic ingredients (e.g., KI, $CuSO_4$). Under the conditions of drying at 50°C, oxidation-reduction reactions could occur that might affect the bioavailability of iron. The Committee considered that this potential problem should be addressed in future experiments.

(5) The method of blood collection by decapitation and draining into a test tube via a funnel raised concerns owing to the potential for contamination by other body fluids (e.g., gastric fluid, spinal fluid, lymph).

(6) The results of lead analyses of blood and tissues of the experimental animals have not been reported. (Dr. Reichlmayr-Lais indicated that such analyses are being attempted in current experiments.)

(7) The possibility that lead supplementation of the basal diet might affect its palatability was not addressed in the experiments, either by pilot trials or by measurements of food intake.

(8) Lead supplementation of the basal diet was performed only at a single (relatively high) concentration of 1 ppm. Further experiments at graded levels of Pb supplementation are desirable in order to establish a dose-effect relationship.

(9) The statistical methods that were used to analyze the data in the two experiments were not described in sufficient detail; the application of multiple t-tests may be a cause for concern, and the various reports contain inconsistencies in numbers of experimental animals per group. These matters might advantageously be clarified in a consolidated report of each experiment. (Dr. Reichlmayr-Lais indicated that such a consolidated report is in press.)

RECOMMENDATIONS AND CONCLUSIONS

In view of the concerns that are listed above, the Committee reached the following conclusions and recommendations:

1. The Kirchgessner and Reichlmayr-Lais data furnish evidence that is consistent with and, in some opinions, indicative of a nutritional essentiality of lead for rats.

2. The evidence is not sufficient to establish nutritional essentiality of lead for rats.

3. To address the basic issue of nutritional essentiality of lead, additional evidence needs to be obtained under different conditions in the laboratory of Kirchgessner-Reichlmayr-Lais, as well as by independent investigators; additional species should also be examined.

The Committee emphasizes the difference that apparently exists between lead concentrations that are of concern from a toxicologic viewpoint and those that might possibly be of nutritional concern. Hence the Committee does not perceive any practical incompatibility between (a) efforts to reduce Pb in the human environment to concentrations that are unassociated with toxic effects and (b) efforts to define the potential nutritional essentiality of lead. The Committee recognizes that current public health concerns for humans are those of lead toxicity.

ATTACHMENT 1

The following materials were considered by the Committee in their deliberations:

1. Reichlmayr-Lais, A. M. and Kirchgessner, M. (1981) Zur essentialitat von blei fur das tierische Wachstum. [Why lead is essential for animal growth.] Z. Tierphysiol. Tierernaehr. Futtermittelkd. 46:1-8.

2. Reichlmayr-Lais, A. M. and Kirchgessner, M. (1981) Depletions studien zur essentialitat von blei an wachsenden ratten. [Depletion studies on the essential nature of lead in growing rats.] Arch. Tierernaehr., 31:731-737.

3. Reichlmayr-Lais, A. M. and Kirchgessner, M. (1981) Eisenkupfer- und zinkgehalte in neugeborenen sowie in leber und milz wachsender ratten bei alimentarem blei-mangel. [Iron-, copper- and zinc contents in newborns as well as in the liver and spleen of growing rats in the case of alimentary lead deficiency.] Z. Tierphysiol. Tierernaehr. Futtermittelkd. 46:8-14.

4. Kirchgessner, M. and Reichlmayr-Lais, A. M. (1980) Lead deficiency and its effects on growth and metabolism. Presented at TEMA-4 Meeting; May; Perth, Australia.

5. Reichlmayr-Lais, A. M. and Kirchgessner, M. (1981) Activities-veranderungen verschiedener enzyme im alimentaren blei-mangel. [Activity changes of different enzymes in alimentary lead deficiency.] Z. Tierphysiol. Tierernaehr. Futtermittelk 46:145-150.

6. Kirchgessner, M. and Reichlmayr-Lais, A. M. (1981) Changes of iron concentration and iron-binding capacity in serum resulting from alimentary lead deficiency. Biol. Trace Elem. Res. 3:279-285.

7. Kirchgessner, M. and Reichlmayr-Lais, A. M. (1981) Retention, absorbierbarkeit und intermeditare neifugbarkeit von eisen bei alimentarem bleimangel. [Retention, absorbability and intermediate availability of iron in the case of alimentary lead deficiency.] Int. J. Vitam. Nutr. Res. 51:421-424.

8. Reichlmayr-Lais, A. M. and Kirchgessner, M. (1981) Katalase- und coeruloplasmin -acktivitat im blut bzw. serum von ratten in blei-mangel. [Catalase and coeruloplasmin activity in blood and serum of rats with lead deficiency.] Zentralbl. Veterinaermed. Reihe A 28:410-414.

9. Kirchgessner, M. and Reichlmayr-Lais, A. M. (1982) Konzentrationen verscheidener stoffwechsel-metaboliten im experimentellen bleimangel. [Concentration of different metabolites resulting from experimental lead deficiency.] Ann. Nutr. Metab. 26:50-55.

10. Reichlmayr-Lais, A. M. and Kirchgessner, M. (1981) Hematologische veranderungen bei alimentarem blei mangel. [Hematological changes in the case of alimentary lead deficiency.] Ann. Nutr. Metab. 25:281-288.

11. Schwarz, K. (1973) New essential trace elements (Sn, V, F, Si): progress report and outlook. Proceedings International Conference Trace Element Metabolism in Animals (TEMA) II. Madison, Wisconsin. Edited by W. G. Hoekstra, J. W. Suttie, H. E. Gantner, and W. Mertz, University Park Press, Baltimore, MD.

12. Pallauf, J., and Kirchgessner, M. (1971) Herstellung der gereinigten halbsynthetischen diat. [Production of the purified semi-synthetic diet.] Z. Tierphysiol. Tierernaehr. Futtermittelkd. 23:128-139

13. Schnegg, A. (1975) Dissertation, T. U. Munchen. Excerpt on diet from Mr. Schnegg's dissertation, provided by Professor Kirchgessner.

14. Kirchgessner, M. and Schwarz, W. A. (1976) Zum einfluss von zinkmangel und unter-schiedlichen zinkzulagen auf resorption und retention des zinks bei milchkühen. [Concerning the influence of zinc deficiency and different zinc additions on resorption and retention of zinc in milk cows.] Arch. Tierernaehrung. 26:3-16.

15. Mertz, Walter (1981) The essential trace elements. Science (Washington, D.C.) 213:1332-1338.

16. Mushak, P. (1982) [Appendix 11-A, draft Air Quality Criteria Document for Lead]. August 9. Assessment of studies reporting the potential essentiality of lead. Available for inspection at U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

17. Kirchgessner, M. and Reichlmayr-Lais, A. M. (1982) [Rebuttal to Appendix 11-A]. September 2. Available for inspection at U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

18. Weil, D. (1982) [Letter to M. Kirchgessner]. October 14. Available for inspection at U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

19. Kirchgessner, M. (1982) [Reply to D. Weil]. October 26. Available for inspection at U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

20. Mushak, P. (1983) [Appendix 12-A, draft Air Quality Criteria Document for Lead]. January 5. Assessment of studies reporting data regarding the potential essentiality of lead. Available for inspection at U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

21. Grant, L. D. (1983) [Letter to M. Kirchgessner]. February 15. Available for inspection at U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

22. Kirchgessner, M. (1983) [Reply to L. D. Grant]. March 28. Available for inspection at U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

23. Grassmann, E., Kirchgessner, M. and Hampel, G. (1970) Zur kupferdepletion bei ratten und kuten mit athylendiamin-tetraazetat und adenin. [Copper depletion in rats and chicks as produced by ethylenediamine-tetraacetate and adenine.] Arch. Tierernaehr. 20:537-544.

24. Grassmann, E. (1976). Zur verwertung verschiedener eisenverbindungen bei der ratte. [The utilization of various iron compounds in the rat.] Zentralbl. Veterinaermed. Reihe A 23:292-306.

25. Schnegg, A. and Kirchgessner, M. (1977) Zur differentialdiagnose von Fe- und Ni-mangel durch bestimmung einiger enzymabtivitaten. [Differential diagnosis of Fe and Ni deficiencies by determining some enzyme activities.] Zentralbl. Veterinaermed. Reihe A 24:242-247.

26. Schnegg, A. and Kirchgesser, M. J. (1977) Aktivitatsanderungen von enzymen der leber und xiere im nickel-bzw. eisin-mangel. [Changes in liver and kidney enzyme activities during nickel or iron deficiency.] Z. Tierphysiol. Tierernaehr. Futtermittelkd. 38:300-205.

27. Schnegg, A. and Kirchgessner, M. (1977) Konzentrationsanderungen einiger substrate in serum und leber bei Ni-bzw. Fe-mangel. [Concentration changes in some serum and liver substrates with Ni and Fe deficiency.] Z. Tierphysiol. Tierernaehr. Futtermittelkd. 39:247-251.

28. Schnegg, A. and Kirchgessner, M. (1977) Alkalische und saure phosphatase-ackivitat in leber und serum bei Ni-bzw. Fe-mangel. [Alkaline and acid phosphatase activity in the liver and serum with Ni versus Fe deficiency.] Int. Z. Vitam. Ernaehrungsforsch. 47:274-276.

29. Nielsen, F. (1983) [Letter to M. Davis]. May 19. Available for inspection at U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

30. Mushak, P. (1983) [Appendix 12-A, draft Air Quality Criteria Document for Lead]. July 1. Assessment of studies reporting the potential essentiality of lead. Available for inspection at U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

ATTACHMENT 2

List of attendees at September 29, 1983 meeting of the Expert Committee on Trace Metal Essentiality:

PANEL MEMBERS

Dr. F. W. Sunderman, Jr. (Chairman)
University of Connecticut, School of Medicine

Dr. Forrest Nielsen
USDA

Dr. M. R. Spivey Fox
FDA

Dr. Orville Levander
USDA

Dr. Walter Mertz
USDA

Dr. Ekhard Ziegler
University of Iowa

Dr. Kathryn Mahaffey*
NIOSH

INVITED DISCUSSANTS

Dr. Paul Mushak
University of North Carolina

Dr. Anna M. Reichlmayr-Lais
Technical University of Munich
Federal Republic of Germany

Dr. E. Grassmann (substituting for Dr. M. Kirchgessner*)
Technical University of Munich
Federal Republic of Germany

EPA STAFF

Dr. David Weil (Meeting Coordinator)
EPA/ECAO

Mr. Jeff Cohen
EPA/OAQPS

Dr. J. Michael Davis
EPA/ECAO

Dr. Robert Elias
EPA/ECAO

Dr. Lester Grant
EPA/ECAO

PUBLIC OBSERVERS

Dr. Gary Ter Haar
Ethyl Corporation

Dr. Elizabeth Lightfoot
Ethyl Corporation

Dr. Jerry Cole
ILZRO

Dr. Magnus Piscator
Karolinska Institute

*not present at meeting

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APPENDIX 12-C

INDEPENDENT PEER REVIEW OF SELECTED STUDIES CONCERNING NEUROBEHAVIORAL EFFECTS OF LEAD EXPOSURES IN NOMINALLY ASYMPTOMATIC CHILDREN: OFFICIAL REPORT OF FINDINGS AND RECOMMENDATIONS OF AN INTERDISCIPLINARY EXPERT REVIEW COMMITTEE

Presented by

Expert Committee on Pediatric
Neurobehavioral Evaluations

To:

Dr. Lester D. Grant, Director
Environmental Criteria and Assessment Office
United States Environmental Protection Agency
Research Triangle Park, North Carolina

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The materials contained in this report were generated as a result of critical evaluations and deliberations concerning the subject studies in the course of review of them by members of the Expert Committee on Pediatric Neurobehavioral Evaluations. The members of the Committee (listed below) unanimously concur with and endorse the findings and recommendations contained in the present report as representing the collective sense of the Committee.

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PREFACE

As part of the periodic (5-year) review and revision of criteria for the National Ambient Air Quality Standards (NAAQS) for lead established in 1978, the EPA Environmental Criteria and Assessment Office (ECAO/RTP) initiated in 1982 an intensive, critical evaluation of pertinent scientific information concerning health effects associated with lead (Pb) exposure. Of considerable importance in that regard are certain published (and related unpublished) studies from several different research groups, which provide data that have been interpreted as demonstrating significant associations between neuropsychologic deficits (e.g., impaired cognitive development) or other neurobehavioral effects (e.g., poorer classroom behavior) and lead exposures in otherwise apparently asymptomatic children. The findings and interpretation of such studies have become a matter of great controversy, especially among those research scientists directly involved in the conduct and reporting of the subject studies.

In an effort to resolve major points of controversy concerning some of the most important and controversial of the subject studies, an interdisciplinary Expert Committee on Pediatric Neurobehavioral Evaluations was convened by Dr. Lester D. Grant (Director of ECAO/RTP) starting in March, 1983, to provide independent peer review of selected studies and to make recommendations concerning how particular study results should be most appropriately interpreted or, possibly, reanalyzed before final interpretation. The Committee comprised internationally recognized experts in the areas of: child development, psychometric techniques, biostatistics, lead exposure measurement techniques, and overall aspects of lead pharmacokinetics and toxicology. The present report contains a series of critiques of interrelated sets of selected studies conducted during the 1970s and early 1980s.

The Committee focused on answering the following four general questions in reviewing each of the sets of studies:

(1) Were the studies appropriately designed and conducted (including data collection and statistical analyses) so as to allow for scientifically sound testing of the main hypotheses posed regarding possible associations between lead exposure and neurobehavioral effects (e.g., poorer classroom behavior, IQ deficits, etc.) in children?

(2) To what extent do the particular data, statistical analyses, and results obtained support the conclusions stated in the published papers (or other related materials regarding each study), and what caveats or limitations should most appropriately be stated as applying to such conclusions?

(3) Are there other conclusions that might be appropriately drawn (given the particular design, data collection, and statistical analyses employed in each study) and/or are there other appropriate approaches to the analysis of the data collected that would be expected to yield further meaningful and important information concerning the hypothesis that low-level lead exposure leads to neurobehavioral deficits in children?

(4) To what extent do the published studies allow for meaningful conclusions to be drawn regarding quantitative exposure-effect or dose-response relationships between any observed neurobehavioral effects and specific levels of lead exposure (as defined by either dentine or blood lead concentrations as indices of exposure)?

In the course of deliberating on general issues such as those posed above, the Committee considered more specific questions or points as appropriate for each of the studies reviewed. Many of the specific questions posed were presented in letters from Dr. Grant to the investigators (see attachment to this report, for a listing of letters). At initial meetings of the Committee in March, 1983, these and other questions were discussed with the senior investigators responsible for the conduct of particular studies, and some additional, unpublished information was provided by the investigators to the Committee to assist in accomplishing as complete an evaluation of each study as possible at the time of review. A preliminary draft of the Committee's report was provided to Drs. Ernhart and Needleman in September, 1983. The Committee reconvened in October, 1983, at which time written comments submitted by Drs. Ernhart and Needleman were considered by the Committee in making revisions in the report.

The Committee members thank the investigators for taking time to meet with us, for their assistance in providing and discussing information beyond that included in the published reports of their studies, and for calling to our attention certain factual errors in the preliminary draft of our report. The Committee hopes that the ensuing critiques of specific studies both (1) help to resolve legitimate controversy regarding the most appropriate interpretation(s) of the subject study results and (2) provide constructive criticisms and recommendations that are of value in carrying out reanalysis of certain subject data sets which hold promise for providing more definitive outcomes than those thus far reported for the studies in the published literature.

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SUMMARY

The Expert Committee on Pediatric Neurobehavioral Evaluations reviewed two independent sets of studies by: (1) Dr. Claire Ernhart and colleagues and (2) Dr. Herbert Needleman and colleagues. The studies evaluated possible associations between low-level lead (Pb) exposures and neuropsychological deficits in children who were otherwise apparently asymptomatic.

The Perino and Ernhart (1974) study evaluated relationships between blood Pb levels in a sample of 80 inner city black children (aged 3-5 yr) and IQ scores determined by the McCarthy Scales of Cognitive Abilities. Small but significant associations between lead exposure and lower IQ scores were reported, based on regression analyses. The Committee found the blood Pb measures were of acceptable reliability, as were also the psychometric measures for children. However, errors now have been discovered in the data analyzed for that report. In addition, confounding variables may not have been adequately measured, and the statistical analyses did not deal adequately with confounding variables. The Committee concludes, therefore, that the study results, as published by Perino and Ernhart (1974), neither confirm nor refute the hypothesis that low-level Pb exposure in children leads to neuropsychologic deficits.

Ernhart et al. (1981), in a follow-up study, reassessed blood Pb levels and neuropsychologic function in a subset of the same children 5 years later. The McCarthy Scales were again used, along with school reading tests and teacher ratings of classroom behavior. Small but statistically significant negative correlations were found between school-age blood Pb levels and scores on some McCarthy subscales, controlling for certain confounders. No significant associations remained if results were deleted for one "outlier" with markedly elevated dentine Pb beyond other values for the higher Pb group. The Committee found the psychometric measures to be acceptable, but the blood Pb sampling method raised questions about the reliability of the reported blood Pb levels. In addition, the statistical analyses did not adequately control for confounding factors. The Committee concludes, therefore, that the Ernhart et al. (1981) results neither confirm nor refute the hypothesis that low-level Pb exposure in children is partially responsible for neuropsychologic deficits. The Committee recommends that longitudinal analyses be carried out, using data from both the Perino and Ernhart (1974) and Ernhart et al. (1981) follow-up studies.

The Committee also reviewed a doctoral dissertation prepared by J. Yamins (1976) under Dr. Ernhart's direction. The Yamins study attempted to replicate certain aspects of the findings reported by Perino and Ernhart (1974), but used different psychometric measures and a different population of children. A major problem was the method of blood sampling, i.e., collection onto filter paper, which requires correction for hematocrit. Hematocrit levels

apparently are not available for data reanalysis. Although Yamins reported small but significant effects of lead exposure on some indices of cognitive functioning (taking age into account), the Committee found it difficult to place much confidence in such findings because of the failure to control adequately for confounding variables (besides age).

Results from an epidemiological study conducted by Needleman and colleagues were reported or discussed in: Needleman et al. (1979), Burchfiel et al. (1980), Needleman (1981), Needleman (1982), Needleman et al. (1982), Bellinger and Needleman (1983), and Needleman (1983). The main set of analyses was presented by Needleman et al. (1979). The study entailed neuropsychologic evaluations for more than 2000 first- and second-grade (mainly white) students. Lead exposure was indexed by dentine Pb in deciduous teeth. The classroom behavior of each child submitting a tooth was rated by the child's teacher. Some children, falling within the highest and lowest deciles for dentine Pb measured in one or more of their teeth, underwent more in-depth neuropsychologic evaluations, including use of an individual standardized measure of intellectual abilities (the WISC-R) to estimate IQ levels and tests of academic achievement, auditory and language processing, visual-motor reflexes, attentional performance, and motor coordination. Needleman et al. (1979) reported a relationship between first tooth dentine Pb values and percentages of students receiving poor classroom behavior ratings, which he has interpreted (Needleman, 1983) as "a strong dose-response relationship." Children in the high-Pb group (top 10% of dentine Pb levels) were also reported to have statistically significantly lower IQ scores (especially verbal IQ) than the low-Pb group (lowest 10% of dentine Pb values), taking into account five covariates in an analysis of covariance. The high-Pb children were also reported to do more poorly on certain other neurobehavioral tasks.

The Committee concludes that the relationship between dentine Pb levels and teachers' ratings of classroom behavior cannot be safely attributed to the effects of Pb, due to: (1) reservations regarding the adequacy of classification of subjects into Pb exposure categories using only the first dentine Pb value obtained for each child and (2) failure to control adequately for effects of confounding variables. The Committee also concludes that the reported results concerning the effects of lead on IQ and other behavioral neuropsychologic abilities measured for the low-Pb and high-Pb groups must be questioned, due to: (1) errors made in calculations of certain parental IQ scores entered as a control variable in analyses of covariance; (2) failure to take age and father's education into account adequately in the analyses of covariance; (3) the failure to employ a reliable strategy for the control of confounding variables; (4) concerns regarding missing data for subjects included in the analyses; and (5) questions about possible bias due to exclusion of large numbers of provisionally eligible subjects from statistical analyses. The Committee concludes, therefore, that the study results, as published by Needleman et al. (1979), neither confirm nor refute the hypothesis that low-level Pb exposure in children leads to neuropsychologic deficits.

The publications by Needleman (1982), Needleman et al. (1982), Bellinger and Needleman (1983), and Needleman (1983) describe further analyses of the same data set reported by Needleman et al. (1979). Burchfiel et al. (1980) reported analyses of certain psychometric data together with additional data on electrophysiological (EEG) measures for a subset of the high-Pb and low-Pb children from the Needleman et al. (1979) study. The above reservations regarding the basic analyses reported by Needleman et al. (1979) apply also to the analyses reported by Burchfiel et al. (1980), Needleman (1982), Needleman et al. (1982), Bellinger and Needleman (1983), and Needleman (1983). Similar reservations apply to analyses of another data set (Needleman, 1981). The Committee recommends that the entire Needleman data set be reanalyzed, correcting for errors in data calculation and entry, using better Pb exposure classification, and appropriately adjusting for confounding factors.

In addition to evaluating the studies of Ernhart and Needleman, the Committee reviewed available reports (some published and others as yet unpublished) of other studies from the United States and Europe. Although an exhaustive, in-depth evaluation of the world literature on low-level Pb exposure was beyond the current charge to the Committee, we note that new studies reported in the spring and summer of 1983, with only a few exceptions, failed to find significant association between low-level Pb exposure and neuropsychologic deficits, once control variables were taken into account.

From its review of the recent research literature covered in this report, the Committee concludes that: (1) in the absence of control for other variables, a negative association between Pb exposure and neuropsychologic functioning has been established; (2) the extent of this negative association is reduced or eliminated when confounding factors are appropriately controlled; and (3) the Committee knows of no studies that, to date, have validly established (after proper control for confounding variables) a relationship between low-level Pb exposure and neuropsychologic deficits in children.

INTRODUCTION

In approaching its task, the Committee was faced first with establishing criteria for research studies, the results of which may be accepted as evidence pertinent to determining the influence of Pb exposures on cognitive functioning in apparently asymptomatic children. Because children live and mature in a complex socio-cultural milieu that affects them in many diverse ways, isolation of a definitive cause, e.g., lead exposure, for neuropsychological problems in children is extremely difficult. Under these circumstances, what kind of research design is necessary or adequate to produce pertinent evidence?

The problem of determining the effects of Pb on cognitive functioning is viewed as an instance of a general class of dosage-response problems. Alternative research designs with which to approach such problems include:

(i) randomized clinical trials;
(ii) cross-sectional observational study of individuals from groups known to vary in exposure (dosage);
(iii) longitudinal study of the same individuals over time;
(iv) a time series of observations on different sets of individuals who are members of groups known to differ in exposure (dosage).

A. Alternative Research Designs

1. Randomized Clinical Trials

There is no question that randomized clinical trials, properly conducted, provide evidence that is highly relevant to the research question. Neither is there any question that the experimental administration of Pb to human subjects is unethical, and not to be considered. This highly effective research design, then, simply cannot be adopted to address the question of the effect of Pb on human cognitive functioning.

2. Cross-Sectional Designs

The bulk of published work assessing Pb effects on human cognitive functioning has entailed the cross-sectional study of a sample of children. A serious complicating feature of the design results from typical empirical findings of association between low or moderate levels of lead exposure, on the one hand, and such background variables as parental IQ, parental education, quality of home environment, family size, etc., all of which are known to be

correlated with children's cognitive performance. Under what conditions, then, might this design yield valid conclusions about the effect of Pb on cognition? Three possibilities appear to exist, as follows:

(a) Were low or moderate levels of Pb consistently found to be negatively correlated with cognitive performance, while all potential confounding background variables were negligibly correlated with cognitive performance, then a valid conclusion would be that Pb is responsible for the cognitive deficits. However, the premise generally appears to be false: published studies on Pb, consistent with research literature in child psychology, report sizable correlations between cognitive performance and a host of background variables.

(b) Were low or moderate levels of Pb consistently found to be negligibly correlated with cognitive functioning, regardless of the pattern of association between cognitive function and confounded background variables, then it would be fairly safe to conclude that the differences in Pb levels are not importantly related to cognitive performance. Again, however, the premise generally appears to be false: most published studies on Pb report significant correlations between Pb and cognitive test scores unadjusted for other key confounders.

(c) Consider a study designed so as to provide a factor analysis of interrelations among variables. It might be found that cognitive performance is represented on one factor along with noncognitive variables that are not appreciably associated with cognitive performance in the absence of Pb. In the presence of Pb, however, such noncognitive variables might be hypothesized to be associated with cognitive function. Lead would be the primary defining variable on such a factor. Noncognitive variables that would be appropriate candidates for this factor analysis include sensory discriminations and electroencephalographic (EEG) recordings. This finding would support the hypothesis that Pb was a partial determinant of cognitive functioning.

The research studies of Pb effects on cognition of which the Committee is aware generally fail to match any of the above conditions (a), (b), or (c). Rather, the studies mainly report cross-sectional data for which: (1) Pb is correlated with cognitive test scores by a nonzero but modest amount; (2) Pb is correlated with background variables; and (3) background variables are correlated with cognitive performance. In most such studies, efforts are made to separate the influence of Pb on cognitive functions from the influence of confounding variables, using methods of statistical adjustment (e.g., regression analysis).

Statistical adjustment for confounding variables may reduce the residual relation between Pb and cognition to a negligible value. If so, however, it would not necessarily follow that cognitive functioning is not influenced by Pb; the effects of Pb might be masked by one or more of the confounding variables. The research design is generally incapable of providing evidence which permits a clear separation of the magnitude of effect of Pb from effects of the confounding variables.

Statistical adjustment for confounding variables may leave a significant residual correlation between Pb and cognition. If so, however, it would not necessarily follow that cognitive function is influenced by Pb. Perhaps other background variables, not explicitly adjusted for, but correlated both with Pb and cognition, are the effective determinants of cognitive differences. Or, perhaps, less fallible measures of the confounding variables would have further reduced the correlation between Pb and cognition to a non-significant amount. The research design is not sufficiently sensitive to provide guidance concerning which of these alternative conclusions should be embraced.

The controversy over the interpretation of results from a series of recent studies may be attributed to this intrinsic ambiguity regarding the assignment of causal status to the predictor variable of interest (Pb) or to confounding variables (e.g., home and parental measures). Some consider Pb to act as a surrogate for the confounding variables. Others consider the confounding variables to act as a surrogate for Pb. There is no scientific basis for accepting or rejecting either set of interpretations.

In view of these considerations, the Committee concludes that, no matter how carefully designed and executed, cross-sectional studies of relationships between Pb and cognitive functioning are not able to yield definitive conclusions regarding the influence of low-level Pb exposures on human cognitive functioning, when measures of both are correlated with background variables also known to influence cognitive development and performance. At best, such cross-sectional studies may yield evidence suggestive of effects of low-level Pb exposures which would need to be confirmed by studies using more definitive research designs.

The Committee has been charged with evaluating the research reports of Needleman and his associates and of Ernhart and her associates. All of these reports concern essentially cross-sectional studies (although some of the Ernhart data are amenable to longitudinal analysis, a subject to which we return later). Each study is thus subject to the severe reservations expressed above: i.e., from cross-sectional studies with confounding variables, it is not possible to draw definitive conclusions about the role of low-level Pb exposures as a determinant of cognition. Nevertheless, we do present more detailed critiques of these studies in sections below, recognizing the importance of attempting to resolve apparent inconsistencies in the results and conclusions presented by these sets of investigators and recognizing, also, the value of accumulating even small or suggestive indications of possible relationships, or lack thereof, between Pb and cognitive deficits.

We have judged that, to assess effects of Pb on cognition, (i) randomized clinical trials cannot be conducted and (ii) cross-sectional observational studies cannot adequately disentangle effects of Pb from effects of confounding variables. We now comment on strengths and weaknesses of certain other research designs, longitudinal studies and time-series analyses, which may be capable of yielding more definitive conclusions than cross-sectional designs.

3. Longitudinal Designs

A longitudinal design is characterized as a study of the same individuals over a period of time. For the topic at hand, primary interest would reside in changes over time in relative levels of cognitive functioning as a consequence of earlier levels of systemic Pb or of changes in systemic Pb. Many (but not all) of the confounding variables are usually quite stable over time, and thus may be assumed to have a similar influence on measures obtained at different times. To that extent, the difficulty created by confounding variables will be at least partially alleviated.

Documentation of the history of systemic Pb exposure should begin early, even prior to an infant's birth. Cognitive performance also should be assessed early, as soon as 18 months after birth. Measurements of both sets of variables should be repeated periodically for several years, and other measures, e.g., dentine lead, might be obtained at appropriate times. It is crucial that as complete a history as possible of Pb exposure (as indexed by changes in internal indices) be obtained and that such indices of exposure be evaluated for relationships to dependent variables indicative of cognitive/behavioral development both proximate and distant in time after the exposure measures are obtained. This is important both to increase information on latency periods for Pb effects to be manifested and in regard to augmenting our knowledge of reversibility/irreversibility of Pb effects.

In the study by Perino and Ernhart (1974) discussed below, the same sample of children was assessed both for Pb exposure and cognitive performance at ages 4-5 years, and again five years later, as reported by Ernhart et al. (1981). The authors did inquire about the relationship between later cognitive measures and earlier Pb levels, but they failed to study the possibly revealing relationship between change in cognitive score and change in Pb levels (see comments on these studies in a later section of this report).

A longitudinal design reduces but does not necessarily totally avoid problems of confounding variables. Variables that remain stable over time for a given individual, while creating difficulty in a cross-sectional design, may not be as much of a problem in a longitudinal design. However, confounding variables that change over time would be troublesome in longitudinal as well as in cross-sectional studies. Techniques for statistical adjustment may (and usually should) be employed for such variables. To the degree that they are prominently

related to Pb levels and cognition or to changes in these variables, they are as troublesome in longitudinal as in cross-sectional studies. The hope is that their effects will be far smaller in longitudinal studies.

4. Time-Series Design

Fortuitous events, from the research perspective, may occasionally provide the opportunity for a time-series study of the effects of Pb on cognitive functioning. For example, it might be recognized that an environmental change is imminent in Community A, a change anticipated to have a large effect on typical systemic Pb exposure in that community. Prior to that change, Pb and cognitive measures might be obtained for a random sample of 5-year-olds (or 7- or 9-year-olds) in community A, and also in community B, considered similar to A except for the impending change. Later, after the environmental change and its effects have had an opportunity to be exerted, similar measures are again collected on random samples at the same age, in both communities. Differential changes in cognition as a function of different levels of Pb may strongly suggest that Pb has influenced cognition. A specific example of where such a research approach might be applied is a situation whereby an imminent governmental or industry action is anticipated that would lead to substantial reductions in Pb exposure in a particular geographic area.

B. Additional Remarks

The Committee cannot conclude these general introductory remarks without presenting an additional caveat regarding the interpretation of even an unambiguous finding of a significant negative relationship between low Pb levels and measures of children's IQ or other behavioral variables, based on epidemiological observations. If an investigator is able to discount the influence of confounding variables, and if no flaws are found with the research design employed or the conduct of the study, the temptation may exist to conclude that Pb is responsible for the observed lowered IQ levels or other behavioral deficits. Note, however, that such results are, in many cases, equally consistent with the conclusion that increased Pb exposures and associated body burdens are a consequence of low IQ or other observed behavioral deficits. Furthermore, knowledge external to the research study generally would not be such so as to provide an obvious basis for preferring one of these conclusions over the other.

REVIEW OF STUDIES BY DR. CLAIRE ERNHART AND COLLEAGUES

A. Background Information

The Committee undertook detailed review of two studies published by Dr. Ernhart and colleagues (Perino and Ernhart, 1974; Ernhart et al., 1981) and, also, preliminary review of a third study reported in the 1976 doctoral dissertation of J. Yamins at Hofstra University. (The latter doctoral research was conducted under Dr. Ernhart's direction but is not yet published in the peer-reviewed literature).

In the first study, based on the doctoral research of J. Perino (under Dr. Ernhart's direction), inner city black children of low socioeconomic status were recruited for study based on blood Pb values obtained during screening for possible undue Pb exposure by the New York City Health Department during 1972. Children were randomly selected to participate in the study so as to represent a group of subjects with lead exposures ranging from low (<30 μg/dℓ) to moderately elevated (40-70 μg/dℓ) according to then existing screening standards. Because the study was designed to evaluate neuropsychologic deficits associated with moderate lead exposures in non-overtly lead-poisoned children, children with histories of overt signs or symptoms typical of Pb poisoning were excluded from the study. Eighty black children (41 boys and 39 girls) of preschool age (3 yr to 5 yr, 1 mo) from Queens, New York, were included in the study. The McCarthy Scales of Children's Abilities (McCarthy, 1972) were administered to the children in their homes by a trained school psychologist (J. Perino), to yield a General Cognitive Scale score with norms obtained in the same manner as and roughly comparable to IQ scores. The test also provided scores on several subscales, i.e. Verbal, Perceptual Performance, Quantitative, and Motor Abilities. Parental IQ was measured by means of the Quick Test (Ammons and Ammons, 1962) of gross intellectual level. Questions regarding other covariates were administered to the parent by the school psychologist, following a standardized format and recording answers on a typed questionnaire form. In general, the results of the study were such so as to lead the authors to conclude that neuropsychologic deficits (i.e., decreased cognitive, verbal, and perceptual performance abilities) were significantly associated with Pb exposure in the otherwise asymptomatic children studied. The results have also been interpreted (in Air Quality Criteria for Lead, U.S. EPA, 1977) as demonstrating such deficits to be associated with Pb exposures resulting in blood Pb levels of 40-70 μg/dℓ.

The study by Ernhart et al. (1981) is a followup study, in which 63 children (30 boys, 33 girls) from the original cohort of 80 black children studied by Perino and Ernhart (1974) were reexamined 5 years later. Scores were obtained for these school-age children on the McCarthy Scales of Children's Abilities, school reading tests, teacher ratings of classroom behavior,

and several neurobehavioral exploratory measures. Hypothesized relationships between performance on these neuropsychologic tests and childhood Pb exposures were first statistically evaluated by means of omnibus multivariate tests (Hotelling's T^2), comparing test scores of "low lead" versus "moderate lead" children defined in terms of (1) pre-school blood Pb levels (low = 10-30 μg/dℓ ; moderate = 40-70 μg/dℓ) and (2)school-age blood Pb levels (low ≤26 μg/dℓ; moderate = 27-49 μg/dℓ). Significant omnibus test results ($p<0.05$) were obtained only for reading scores related to both preschool and school-age Pb levels. Further multivariate and univariate analyses were conducted for these significant neuropsychologic outcome variables. Univariate tests for differences on McCarthy scores between low and moderate Pb subjects (ignoring control variables) suggested that the moderate Pb group performed more poorly on the General Cognitive Index (GCI) and 3 of the 5 McCarthy Test subscales. However, multivariate (regression) analyses revealed that sex and parental IQ were control variables that were significantly correlated with one or more outcome measures. When these control variables were ignored in analyses including Pb exposure measures, preschool Pb was significantly negatively related to scores on the GCI, 4 of 5 McCarthy subscales, and the reading tests. When sex and parental IQ were taken into account, however, preschool Pb was not related to any neuropsychologic outcome measure and school-age Pb was significantly related only to the McCarthy GCI, verbal subscale, and motor subscale scores (with the variance attributable to school-age Pb generally being less than half that found for the same outcome measures when the control variables were excluded). Dentine Pb levels in shed deciduous teeth of 33 children were not significantly related to any outcome measures, even when control variables were ignored.

The Yamins (1976) dissertation study, in part, attempted to replicate the Perino and Ernhart (1974) findings, using a different study population and psychometric tests. Preschool children (aged 2 yr, 4 mo to 5 yr, 9 mo), including 80 black (38 girls, 42 boys) and 20 white (10 girls, 10 boys) children from low to low-middle socioeconomic status communities in the Nassau County (Long Island) Department of Health Clinics lead-screening program catchment area, were included in the study. Children with overt signs or symptoms of Pb intoxication were excluded. Of the included children, 54 black subjects had blood Pb levels below 37 μg/dℓ, whereas 26 fell in a 38-70 μg/dℓ range; of the 20 white children, 19 had blood Pb levels below 37 μg/dℓ. Cognitive performance and language development of the children were assessed by the following tests administered in a set sequence in the home by a school psychologist blind as to the children's Pb levels: a "nonverbal" IQ test (Peabody Picture Vocabulary Test; PPVT); a general information test (Caldwell Preschool Inventory); a concepts test (Block Sort); a perceptual-motor functioning test (Copy Forms); and a sentence repetition task designed for the study. The Ammons Quick Test was used to measure parental IQ, and data were gathered on several other background variables (parental education and occupation, quality of housing,

child's medical history, number of siblings, etc.) by means of standardized questionnaire and rating forms. Raw scores for all dependent variable measures were used in multiple regression analyses, which took into account age as well as the other potentially confounding background variables that were measured. For the black children, several such variables (e.g., parental IQ and education, absence of father from home, etc.) were significantly negatively related to children's Pb levels but positively related to each other and the children's cognitive and language variables. Similar results were obtained for the white children. Stepwise multiple regressions were then performed, excluding predictor variables contributing less than 1% of the variance, entering the included predictor variables into the equation before Pb. With all predictor variables controlled, for the black sample, Pb contributed 2.4% of the total variance for nonverbal intelligence (PPVT, $p<0.05$), 3.1% for general information (Preschool Inventory, $p<0.01$), 2.4% for overall level of acquired syntax (Total Repetition Score, $p<0.05$), and 2.5% for ability to repeat nongrammatical verbal stimuli (Ungrammatical Stimuli Test, $p<0.05$). Lead did not contribute significantly to conceptual level (Block Sort), perceptual-motor functioning (Copy Forms), or ability to repeat grammatical stimuli (Grammatical Repetition) scores.

In order to evaluate critically the above studies, the Committee met with Dr. Ernhart at EPA facilities in Research Triangle Park, NC on March 17-18, 1983. At that time, a summary overview presentation was made by Dr. Ernhart on the objectives, design, data collection and analysis procedures, and results for each of the studies. Certain listings of raw data values (provided in coded form to protect the privacy of subjects) and other pertinent published and unpublished materials were examined by the Committee and considered during discussions with Dr. Ernhart regarding diverse aspects of the studies reviewed. Some additional, follow-up information was requested by the Committee and was provided to them subsequent to the March 17-18 meeting with Dr. Ernhart. See Attachment 1 for a list of materials examined by the Committee in connection with their review of the subject studies. The Committee's comments regarding the most salient points of concern and controversy related to methodological and other features of the above studies by Ernhart and associates are presented below.

B. Comments on Perino and Ernhart (1974) and Ernhart et al. (1981) Studies

1. Indicators of Lead Exposure

In the first two studies under consideration, Perino and Ernhart (1974) and Ernhart et al. (1981), the major indicator of exposure was blood Pb, with additional use of erythrocyte porphyrin (EP) measurements and a sub-group of dentine Pb samples in the follow-up study of Ernhart et al. (1981).

On the basis of current criteria of methodology assessment for Pb analyses as noted in Chapter 9 of the EPA draft document Air Quality Criteria for Lead (U.S. EPA, 1983), it can be said that the blood lead values in the Perino and Ernhart study are reasonably reliable. With the follow-up study of Ernhart et al. (1981), blood lead accuracy becomes potentially problematical, due both to: (1) a combined positive bias of capillary blood sampling and choice of analysis, and (2) a bias of negative direction but of possibly variable size, owing to the generally poorly recognized effect of whole blood hematocrit/hemoglobin on blood Pb measurements using filter paper. The latter factor requires making use of the hematocrit measurements for the subjects' blood (which presumably are available, since EP measurements also require knowing the hematocrit) to correct for differential spread or diffusion of blood (and concentration of Pb therein) on the filter paper matrix.

Measurement of Pb in dentine of shed teeth from the subjects in the Ernhart et al. (1981) follow-up study was carried out in the laboratory which both pioneered the analysis of Pb in teeth and probably has the most experience and proficiency with such analyses. The method of analysis for dentine Pb is reasonably reliable, and it appears that analysis error in replicate sampling is at the step of isolating the dentine zones from a given whole tooth sample.

Measurement of erythrocyte porphyrin involved blood collected on filter paper and subsequent elution and micro-fluorometric analysis. Such a "wet" or laboratory analysis is considered much more reliable than the use of the hematofluorometer when applied to blood samples of modest EP content. Analytical error was noted to be less than 15 percent.

In the study of Perino and Ernhart (1974) lead exposure in the pediatric subjects was indexed by analysis of venous whole blood. Characteristics of the specific procedures employed and pertinent evaluative comments are as follows:

(a) Venous blood samples were collected by trained technicians in a lead screening program and analyzed in the laboratory facilities of the New York City Department of Health (NYCHD) during the summer of 1972. Sampling involved standard precautions to minimize sample contamination and collection during the summer months, when blood lead values in the city are known to be maximal. Samples were analyzed within 48 hours of collection and refrigeration.

(b) As a lead analysis facility, the NYCHD laboratory has processed a large volume of samples for lead content over many years, an important consideration in view of the fact that laboratory proficiency is directly related to the level of Pb analysis activity.

(c) The specific method of blood lead analysis employed was the Hessel extraction variation of atomic absorption spectrometry (Hessel, 1968), a macro method

using venous blood which still enjoys popularity up to the present time. The periodic surveys by the Centers for Disease Control (CDC) of participating laboratories in their proficiency programs indicate (see Boone et al., 1979) that the Hessel method is somewhat more accurate than the Delves cup technique and more accurate than the other variations of atomic absorption spectrometry. Precision tends to be less than for the Delves cup procedure, consistent with the reported analytical error of ±5-6 μg Pb/dℓ for the NYCHD laboratory when using the Hessel method (communication of B. Davidow to N.B. Schell, see Ernhart, March 11, 1983: summary of conversation between N.B. Schell and C. Ernhart). Compared to isotope dilution mass spectrometry (IDMS), the Hessel method for the range of blood lead in the Perino and Ernhart study shows a modest positive bias of 2.5 μg Pb/dℓ.

(d) At the time of data collection for the Perino and Ernhart study, it was the practice of the NYCHD laboratory to report blood lead values rounded to the nearest decile of blood lead. Hence, a subject blood Pb value of 40 μg/dℓ in the Perino and Ernhart (1974) report would have resulted from a reading of some value between 35 and 44 μg Pb/dℓ.

(e) Internal and external quality control protocols were in place in the NYCHD laboratory at the time of the subject study. The latter consisted of participation in both the CDC and New York State proficiency testing programs, and the NYCHD laboratory met acceptable proficiency standards.

(f) It appears that there are no major difficulties with methodological aspects of the blood Pb data. The moderate positive bias in the Hessel procedure, if corrected for among the Perino and Ernhart (1974) study data, would result in a constant shift downward in all values. Since there was decile rounding, absolute corrections for this bias would require having the original blood Pb values.

(g) The full use of confidence bounds for the lead measurements, if employed in any overall reanalysis of the data, would require having the original blood lead values as well as taking into account the analytical error noted above.

Lead exposure levels for subjects in the follow-up study of Ernhart et al. (1981) were indexed via measurement of Pb in capillary blood (applied to filter paper) and free erythrocyte protoporphyrin (FEP) determination. A sub-group of the follow-up population furnished shed teeth for dentine lead analysis. Characteristics of the procedures used and evaluative comments are as follows:

(a) Capillary blood samples were collected on filter paper and analyzed in the same NYCHD laboratories (as noted above) that assayed blood Pb by the Delves cup variation of atomic absorption spectrometry.

(b) It is now generally accepted that capillary blood samples, as compared to those obtained by venous puncture, manifest a significant positive bias in lead level even under relatively stringent sample collection conditions. The best data base by which to estimate the magnitude of this positive bias is the NHANES II survey, which indicated that for the Delves cup procedure used in the present study under discussion capillary blood Pb was 6 μg/dℓ higher than for venous samples. An additional positive bias of approximately 3 μg/dℓ exists for the Delves cup analysis compared to the definitive IDMS method.

(c) A generally unrecognized problem with the analysis of lead in blood using filter paper spotting has to do with the close dependence of blood flow (on filter paper) on hemoglobin/hematocrit content. The study of Carter (1978) makes it clear that blood flow is increased on filter paper with decreasing hematocrit, resulting in proportionately lower blood lead values contrasted to venous blood analysis.

(d) In view of the documented problem of using blood on filter paper without correction for hematocrit, blood lead values in the Ernhart et al. (1981) report would have to be appropriately corrected, if this was not already done initially by the NYCHD. It should be noted that Carter (1978) observed underestimation of lead content of blood on filter paper at hematocrit values that would be considered in a normal range.

(e) Dentine lead levels were determined in the laboratories of Dr. Irving Shapiro, School of Dental Medicine, University of Pennsylvania, a facility which pioneered such analyses and is recognized as having the most proficiency in such measures. In this study, dentine was isolated from a given whole tooth sample.

(f) Samples of isolated dentine were dissolved in perchloric acid, buffer added, and lead measured by an electrochemical technique, anodic stripping voltammetry. At the levels of lead being measured in the dentine samples, this technique provides reasonably reliable results for the solubilized analyte.

(g) From data of Shapiro et al. (1973), duplicate analysis of dentine with low and elevated lead exposure of subjects indicates that the analytical error increases with concentration, suggesting greater variation in replicate sectioning than in the instrumental measurement itself.

(h) Identification of an "outlier" by Ernhart in further unpublished analyses of data from the follow-up study (see following sections) was done on the basis of a dentine lead value being 107.4 ppm Pb in the subject sample. A methodological problem accounting for this high value has been discounted by Shapiro (personal communication of I. M. Shapiro to C. B. Ernhart, see Ernhart, February 3, 1983, letter to D. Weil), who indicated that any contamination of the dentine section by inclusion of circumpulpal dentine, a region manyfold higher in lead, would only account for 3-4 percent of the above dentine lead level.

(i) Erythrocyte porphyrin analysis in the present study was carried out in the NYCHD laboratory which simultaneously analyzed capillary blood for lead. It was noted that analytical error was less than 15 percent, using a microfluorometric analysis of blood samples eluted from the filter paper. This laboratory employs internal and external quality control protocols for EP analyses, the latter including the EP proficiency testing program of CDC.

2. Psychometric Measurements and Procedures

Comments on the psychometric measurements employed in the Perino and Ernhart (1974) study and the results obtained are as follows:

(a) The study employed the McCarthy Scales to assess the intellectual development of young children and the Ammons Quick Test to assess parents' IQ levels. The Committee agreed that the McCarthy Scales were appropriate for assessing intellectual abilities of the children in this sample, whose race, age range, and socioeconomic status (SES) were represented in the standardization sample. The Ammons Quick Test, however, has more questionable validity for two reasons: (1) the content of the test is a very limited sample of adult intelligence, and (2) the test was not standardized on low SES black subjects. The reliability of the McCarthy Scales is satisfactory for the present research. The reliability of the Quick Test, however, is only about .75, a low value for an adult measure. More importantly, correlations with the Stanford-Binet and WISC range from only .10 to .80, with a median in the .40 range. Large discrepancies have been observed between Quick Test Scores and individual IQ test scores (Sattler, 1982). Although the Quick Test is considered useful in large scale research studies, where a simple and quick assessment of average ability is needed, the measure is less adequate in the Perino and Ernhart study where it was used as a

control for individual differences. A measure such as the short form of the WAIS or the WAIS vocabulary scale would have provided a better estimate of parental IQ.

(b) The administration of the tests by the first author, a school psychologist, was blind with respect to the children's blood Pb levels. Although the tests were administered in the home, under nonstandard conditions, the Committee concluded that the assessments were generally valid. Because of the training and clinical experience of the investigator, the Committee thought it unlikely that the assessments were seriously compromised.

(c) Birth weight, history of birth risk factors, and maternal education were reported by the mothers in an interview, but were not verified by checking of appropriate records. Maternal occupation was recorded from clinic records employing a 1950 census classification that was inadequate to differentiate among urban blacks. Thus, nearly all families in this sample fell within two occupational classes. It is not known whether a finer SES scale would have resulted in greater relations between SES and other variables in the study than those reported by Perino (1973).

(d) In view of the limitations of the Quick Test and the measurements of some of the control variables, it is especially important that new analyses of the data (proposed below) be employed to maximize the efficiency of the control variables.

(e) Descriptions of quality control procedures by Dr. Ernhart regarding the checking of data entries onto computer cards and/or tapes seemed to indicate that reasonable care was taken to ensure accurate encoding of data for statistical analyses. The Committee had no feasible way to confirm this independently, but Dr. Ernhart, in responding to the Committee's request for reanalyses of the data set, reported as follows: "In the course of conducting the reanalyses to include parent education, we found several errors in the data and the previous analyses. One child's age was incorrect by one year (38 months rather than 50 months). This changed his General Cognitive Index (GCI) from 50 to 86; other scores were correspondingly affected. Another child's GCI was incorrect by one point. The degrees of freedom used and reported in the tests of significance of the lead effect (regression analyses) should have been 1 and 75, not 4 and 75."

Comments on the psychometric assessment procedures used by Ernhart et al. (1981) in the follow-up study are as follows:

(a) Because this study is a follow-up of the Perino and Ernhart sample, many of the issues raised about the original study apply here. Also, use of the McCarthy Scales with age groups not included in the standardization sample is questionable. More than half of the children were beyond the age range of the test, and their test scores were determined by linear extrapolation. The Committee believes that a better procedure would have been the use of residuals after regressing raw McCarthy Scale scores on age at testing. The Committee acknowledges that no subject reached the ceiling on the subtests and also that some value exists in re-administering the same measure in a longitudinal study. However, the Committee concludes that it would have been preferable to have chosen an age-appropriate measure of intelligence, such as the WISC-R, which is based on a suitable standardization sample and also taps cognitive performance of older children. Despite reservations about the use of the McCarthy Scales in the follow-up, the Committee does not believe that the assessment of intellectual development was seriously compromised. Because the children in the study were functioning at levels well below those of most children of their ages, the test was more appropriate for them than for most children of the same age but of average intelligence.

(b) Reading test scores were obtained from many different tests. The Committee concludes, however, that the combination of multiple measures does not necessarily compromise the assessment of reading achievement (Scarr and Yee, 1980). The age correction used was appropriate.

(c) More than one psychologist collected the follow-up McCarthy data, generally within the children's schools. The Committee believes that the administration and scoring of the protocols were adequate. The testers were both blind as to the children's Pb levels and well-trained in psychometric assessment.

(d) Correlations between the earlier and later administrations of the McCarthy Scales, as reported in Ernhart et al. (1980), were in the moderate range (from .24 to .61). The highest correlation is for the General Cognitive Index, which is considered by the Committee to be the most important cognitive measure in the study. In light of developmental changes from preschool to school-age skills, and the use of extrapolated scores, this relationship suggests considerable reliablity for the McCarthy Scales in the follow-up study.

(e) The same comments regarding quality assurance checks for data entries as were made under (e) above for the Perino and Ernhart (1974) study also apply here.

3. Statistical Analyses

The Committee believes that the treatment of confounding factors can be handled in a better way than as described in the 1974 and 1981 Ernhart papers. The analyses performed by Ernhart and colleagues can be questioned in light of currently accepted statistical practices for dealing with interaction and confounding, and they should be reworked.

The proper model for assessing the effect of Pb exposure on IQ is one which contains, in addition to the Pb exposure variable, all factors deemed to be potentially confounding. A potentially confounding factor is one which is correlated (in the population) with the exposure variable (Pb) and for which there is reasonable evidence from previous research experience and knowledge that it is predictive (in its own right) of the outcome variable (IQ). Thus, a procedure which chooses potential confounders via a forward selection procedure, ignoring the Pb variable (as Ernhart did), can be misleading and can actually incorrectly drop important confounders from consideration. A backward elimination strategy is designed to obtain the most accurate estimate of the effects of the exposure variable adjusted for all key confounders, whereas a forward selection approach is designed to predict the outcome variable but does not assure an accurate estimate of the effects of the exposure variable.

As an example, parental education was eliminated by a forward selection approach not involving the Pb exposure variable at all; in fact, it is a potential confounder, and should only be eliminated from the full model if its elimination does not alter the Pb exposure regression coefficient. Similarly, SES should be handled in the same fashion.

In theory, assuming that the data set is free from bias (i.e., is a random sample of the population under study), one can lose precision but not validity by including in the full model a true non-determinant of the dependent variable under study. An example in the data under consideration is the variable sex, which is generally agreed to be a predictor of motor skills but not of the other outcome measures being studied. Its inclusion in the full model (using any outcome variable other than motor skills) should not cause a validity problem (even though it is correlated with Pb exposure); this can be demonstrated (assuming that the data are representative of the population) by dropping the sex variable from the full model and noting that the Pb exposure coefficient does not materially change. With motor skill as the outcome variable, sex should be expected to be manifest as a real confounder in these data and hence cannot be dropped from the model. In summary, then, a reanalysis of the Perino and Ernhart (1974) and Ernhart et al. (1981) data should be carried out, based on a model containing the Pb exposure variable and all available confounders measured.

In general, interaction effects between the Pb exposure variable and the covariates should be assessed before confounding issues are considered. A qualitative assessment can be

done initially by stratifying on each of the covariates and determining whether the relationship between Pb exposure and IQ is reasonably constant across strata of the covariate under consideration. Nonconsistency suggests the need for one or more interaction terms in the model under study. Ultimately, the modeling of interaction involves the use of cross-product terms in regression models. A strategy for dealing with interaction and confounding in observational epidemiologic data is described by Kleinbaum et al. (1982). Possible interaction effects were not really examined by Ernhart and colleagues, and the presence of any interaction(s) would complicate data interpretation. However, given the highly variable nature of the data and the limited sample size, it may be difficult to deal adequately with interaction assessment for these data.

Comments on specific aspects of the statistical analyses employed in the 1974 and 1981 Ernhart studies include:

(a) Corrections for unreliability (i.e., measurement error) in the variables under study should be made, especially concerning the Pb exposure indices. Such corrections will adjust the observed correlations, and could have a major impact on the ultimate conclusions drawn from the analyses. They provide a limit on the strength of relationships by showing the relationship that would be expected were the measurements made and recorded without error.

(b) The outlier alluded to earlier in the Ernhart et al. (1981) data set should be dropped from all analyses. The dentine Pb value provides enough evidence that, in this case, the past Pb exposure was sufficiently high to conclude that the subject may have earlier been overtly symptomatic but undiagnosed.

(c) It is important that the dependent variables be adjusted appropriately for age. As a suggestion, one could use, for each child, the deviation from the linear regression line of "raw score" on "age at testing".

(d) Dependent variable scores for a given individual on a series of intelligence tests are obviously correlated. Multivariate analysis of covariance is one option, but must be done very carefully. Certain assumptions (e.g., multivariate normality) must hold at least approximately.

(e) Treating the Pb exposure variable as a continuous variable is preferable to categorizing cases into high and low Pb groups.

(f) The Committee notes that, for the 62 children in the 1981 study (excluding the outlier), significant correlations are seen between the identification number

assigned to children and other variables of interest. Identification number correlates -0.43 with 1972 level of blood Pb, 0.38 with parent IQ, 0.28 with parent education, and 0.27 with 1972 GCI score from the McCarthy scale. These results would be expected if identification numbers were assigned to children in the order in which they were assessed (by Perino in 1972) and if the children with higher Pb levels tended to be the earlier ones assessed. Results of the Ernhart studies, particularly the one by Perino and Ernhart (1974), could be affected by this nonrandom ordering of assessments, to the extent that any aspects of the assessment process systematically changed over the course of the studies.

An alternative research question to those addressed in the Perino and Ernhart (1974) and Ernhart et al. (1981) analyses can be asked by considering data from the cases assessed both in 1972 and in 1977: namely, is there a relationship between differences in cognitive scores and differences in blood lead concentrations from 1972 to 1977? Do children whose blood lead levels were higher in 1977 than expected from their 1972 levels display cognitive scores in 1977 that differ from those expected from their 1972 cognitive scores?

This question could be addressed by regression analyses. The 1977 Pb level could be predicted from its regression on the 1972 Pb level and residual values obtained. Similarly, the 1977 IQ value could be predicted from its regression on the 1972 IQ value and residual values obtained. The correlation between IQ residuals and Pb residuals would indicate an association between change in IQ and change in Pb. That correlation also could be adjusted for confounders such as parental IQ, parental education, and SES. We would urge such a reanalysis of the data from Perino and Ernhart and Ernhart et al. (after correction of the erroneous values recently discovered in those data). Interpretation of results from such analyses must depend upon careful inspection of the cross-lagged correlations on which the correlation of residuals depends. In addition, of course, even the residual values may be acting as surrogates for unrecognized confounding variables.

4. Committee Conclusions and Recommendations

The Committee's conclusions and recommendations regarding the Perino and Ernhart (1974) study can be summarized as follows. Blood lead levels, as the main index of exposure, appear to be of acceptable reliability. The psychometric measures for children are also acceptable, but confounding variables may not have been adequately measured. The statistical analyses do not adequately deal with confounding variables. In the view of the Committee, the findings of

this study, as reported, neither support nor refute the hypothesis that low to moderate lead exposures are associated with cognitive impairments in apparently asymptomatic children. The Committee recommends that the data from the Perino and Ernhart study be used in conjunction with the 1981 Ernhart et al. follow-up study in longitudinal analyses.

The Committee's conclusions and recommendations concerning the Ernhart et al. (1981) study include the following points. Given limitations in both the control and the outcome measures, it is difficult to assess the possible role of less-than-ideal measures in contributing to the generally null results reported. When the authors conclude that there are no significant effects, or very weak effects at best, then that outcome might also be reasonably attributable to unreliable measures or other procedural problems. One major difficulty with this study is the potential unreliability of the blood Pb level measurements, such that the Committee recommends that the blood Pb values be corrected in the fashion specified earlier. The psychometric data were adequately collected but should be readjusted for age. The cross-sectional analyses suffer from the same problems as those of the previous (Perino and Ernhart, 1974) study. More importantly, the analyses failed to exploit fully the longitudinal aspects of the study data set. In the view of the Committee, then, the findings of this study as reported in the published form also neither support nor refute the hypothesis that the reported blood lead levels are associated with cognitive impairments in children. The Committee strongly recommends that longitudinal analyses of these data (from both Perino and Ernhart, 1974, and Ernhart et al., 1981) be carried out.

C. Comments on Yamins (1976) Dissertation Study

1. Indicators Of Lead Exposure

Comments on specific aspects of the Pb exposure measurement methodology used in the Yamins (1976) dissertation study are as follows:

(a) Blood Pb was sampled by finger puncture, using established techniques for blood lead sampling, and the blood samples collected on filter paper presumably provided by the New York City Health Department. Upon collection, samples were transported to the New York City Health Department for lead measurement.

(b) The use of filter paper for blood collection raises the same question that is of concern in the Ernhart et al. follow-up study, i.e., the blood lead value must be corrected for hematocrit. The problem here occurs, actually, with each of the three indices (highest blood lead, mean blood lead, or most recent blood lead), so that it is not possible to assess the actual blood lead level in each

case nor to determine the suitability of selecting one exposure index over another, since a given subject may have had variable hematocrit over the multi-sampling time period.

(c) Measurement of EP was also carried out in the laboratories of the New York City Health Department, quality control details for which were discussed among comments on the studies of Ernhart and coworkers (vide supra).

2. Psychometric Measurements and Procedures

In the Yamins dissertation, a variety of psychometric measurement procedures were employed, including some standardized instruments such as the Caldwell Preschool Inventory and other, more-or-less experimental measures such as the verbal repetition tasks.

Specific comments on the psychometric measurements utilized by Yamins (1976) include:

(a) This study employed the Peabody Picture Vocabulary Test (PPVT) to assess the intellectual development of the children. The PPVT is not a nonverbal measure of intelligence; it provides a narrow assessment of verbal abilities. However, the committee agreed that the PPVT was a reasonable measure of cognitive performance to use in the study because the scores correlated well with the other cognitive and experimental language measures, including the Caldwell Preschool Inventory, which is an appropriate measure for this population.

(b) The Ammons Quick Test was used to assess parental IQ in this study. As noted earlier, this measure has questionable validity. However, the pattern of correlations between the Quick Test scores and other variables does establish some credibility for its use in the current study.

(c) The experimental measures of language skill correlated with child's age, as one would predict, and yet appear to measure skills already tapped by the cognitive measures.

(d) There is no obvious explanation for the correlation of 0.30 between parent Quick Test scores and child's age. However, when age is partialled out, the correlation between child IQ and parental IQ is approximately 0.35, a value close to that found in other studies.

(e) The author (Yamins) administered all of the cognitive and language measures in the children's homes and was blind as to Pb levels at the time. She appears to have been appropriately trained and competent to collect the psychometric test data. Quality assurance checks regarding data collection (e.g., scoring, coding, and keypunching) could not be ascertained but are assumed to be the same as for the above Ernhart studies.

3. Statistical Analyses

Many of the same reservations expressed earlier regarding the analyses used in the 1974 and 1981 Ernhart studies also apply here. Specific concerns include the following:

(a) Stepwise multiple regression was employed to choose the set of covariates to be included in the final regression model with mean lead level. In the Committee's view, this is not the appropriate way to deal with potentially confounding factors. A backward elimination strategy starting with a model containing lead and all potential confounders is recommended since confounding involves association with both the outcome variable (e.g., a measure of learning performance) and the exposure variable (e.g., mean lead level). A forward selection approach, as was apparently employed by Yamins, ignores the relationship between the potential confounders and the exposure variable in choosing an appropriate subset for control, and hence can lead to inappropriate adjustment.

(b) The strategy for analysis described on page 79 of the Yamins (1976) dissertation is not appropriate for valid control of confounding effects (see preceding comment). Although it may produce the same results as a backward elimination approach, one cannot know without trying both approaches. In this case, backward elimination of variables does not markedly alter the outcome of the analysis. One Committee member (LH) found that the association between Pb and IQ remained after controlling for father's absence, parental IQ, parental education, birth order, and birth weight, using a backward elimination approach.

(c) The results displayed in Table 9 (page 82) of the dissertation do not, in the Committee's opinion, represent a strong indictment of lead exposure. Finding a few significant partial correlations of lead exposure with various dependent variables just by chance is not at all unlikely when performing several analyses using mutually correlated dependent variables. Apparently, no multivariate (as opposed to multivariable) analyses were employed to account for such correlations.

(d) The results in Table 10 (page 85) of the dissertation are based on a comparison of a "low lead" group to a "moderate lead" group (after dichotomizing lead exposure), with adjustment only for the covariate "age". Given that other potential confounders were apparently ignored, and given that several comparisons were made involving correlated responses, not much importance can be attached to the few significant findings reported.

(e) Results presented in Tables 11 (page 86), 12 (page 88), 14 (page 91), and 15 (page 93) of the dissertation are also based on controlling only for age. The Committee finds it difficult to place much importance on the findings presented in these tables.

4. Committee Conclusions and Recommendations

The Committee concludes that, despite reservations expressed regarding psychometric measurements employed in the Yamins study, the pattern of results obtained (including the intercorrelations between different measurement outcomes and parental measures) lends credibility to the psychometric results as reasonably reflective of the cognitive abilities of the subjects tested. The blood lead data require correction for hematocrit because of the use of filter paper for blood collection; unfortunately, the hematocrit values are not available to make this correction. In addition, the Committee finds that specific statistical analyses employed (including stepwise regressions and covariate analyses controlling only for age) are not the most appropriate for analyzing the Yamins data set. Rather, multivariate analyses should have been used that included other potential confounders besides age and, also, backward elimination of variables having negligible impact on the variance attributed to Pb. The Committee further finds that the very modest residual effects attributed to Pb based on the reported analyses controlling only for age are not convincing evidence for a negative effect of Pb on the cognitive abilities of the subject children.

REVIEW OF STUDIES BY DR. HERBERT NEEDLEMAN AND COLLEAGUES

A. Background Information

The Committee undertook detailed review of an epidemiological study published in 1979 by Dr. Herbert Needleman and associates (Needleman et al., 1979). In addition, limited review was carried out for several other reports (Burchfiel et al., 1980; Needleman, 1981; Needleman, 1982; Needleman, 1983; Bellinger and Needleman, 1983) published as follow-up analyses of the same data set and/or new data constituting extensions of the 1979 study.

Approximately 3329 children attending first and second grades between 1975 and 1978 in Chelsea and Somerville, Massachusetts, constituted the study population in the Needleman et al. (1979) study. Children submitted shed teeth to their teacher, who verified the presence of a fresh socket. The shed deciduous teeth were cleaned ultrasonically (discarding any containing fillings), followed by dissection of a 1-mm central slice and subsequent analysis of Pb in dentine tissue by anodic stripping voltammetry. Teeth were donated from 70% of the population sampled. Almost all children who donated teeth (2146) were rated by their teachers on an eleven-item classroom behavior scale. The results obtained for the rated children were reported to demonstrate a dose-response relationship between increasing dentine Pb levels and increasing percentages of students receiving negative (poorer) ratings on several of the 11 categories of classroom behavior, as shown in figure 1 below.

Following the teachers' ratings of classroom behavior, subsets of the rated students (reported to represent polar groups of children with the lowest and highest 10 percent of dentine Pb levels) were recruited for further, extensive neuropsychological evaluation by means of psychometric tests. Each subject whose initial tooth slice was in the highest 10th percentile (>24 ppm) or lowest 10th percentile (<6 ppm) was provisionally classified as having high or low lead levels, respectively. Repeat dentine lead samples from the same teeth were analyzed, when possible, and attempts were made to obtain and analyze other shed teeth from each subject provisionally classified in either lead exposure group (with more than one analysis being obtained for all but one subject). Parents of children provisionally classified as having either high or low dentine Pb levels were invited to have their children participate in further neuropsychological evaluations. Criteria were established for requisite agreement between replicate dentine sample analyses before the data for a given subject were included in the study; when requisite agreement was not found, then the subject was designated as "unclassified" and excluded from data analyses. Other children were excluded from the study because: (1) their parents were unable or unwilling to participate; (2) they came from bilingual homes;

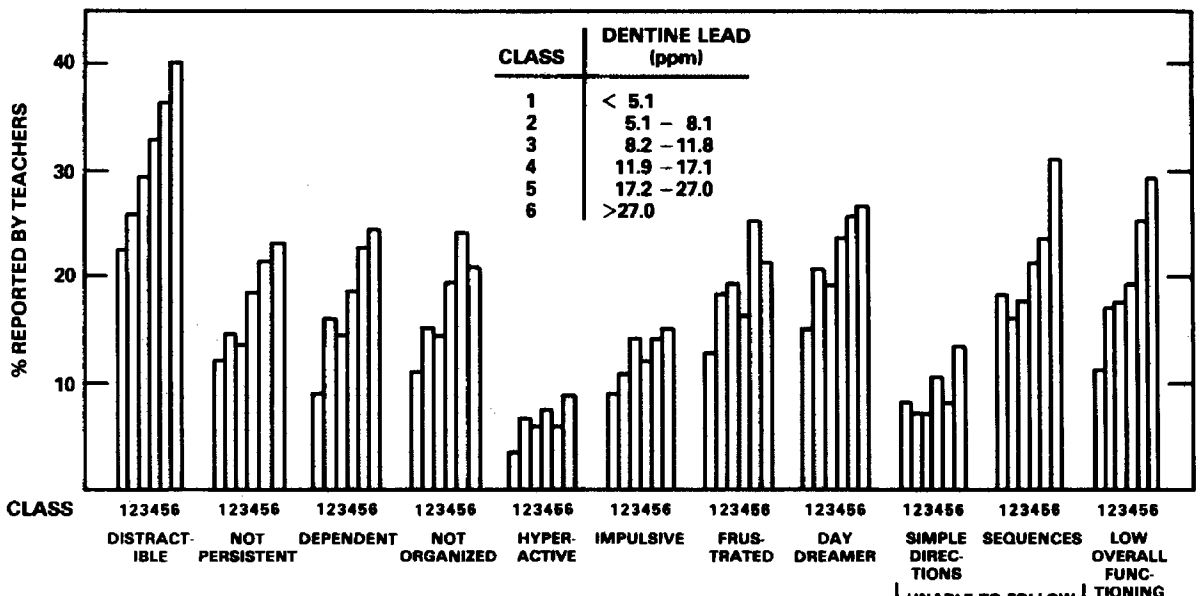

Figure 1. Distribution of negative ratings by teachers on eleven classroom behaviors in relation to dentine lead concentrations.

Source: Needleman et al. (1979).

(3) they had been diagnosed as having been lead poisoned; or (4) their medical history indicated a birth weight of <2500 g, delay in discharge beyond mother's discharge from hospital after birth, or a record of noteworthy head injury (any of which can correlate with slower neurobehavioral development). Table 1 from the Needleman et al. (1979) paper, reproduced below, lists the number of provisionally eligible children, those excluded from neuropsychologic testing, and those undergoing neuropsychologic testing who were retained or excluded from data analyses.

TABLE 1. REASONS FOR EXCLUDING SUBJECTS AND DISTRIBUTION OF FINAL DENTINE LEAD LEVELS IN INCLUDED AND EXCLUDED GROUPS

GROUP		NO.	DENTINE LEAD LEVEL		
			LOW	HIGH	UNCLASSIFIED
Provisionally eligible subjects:		524	258	187	79
Excluded from neuropsychologic testing:		254*	123	101	30
Bilingual home	84				
Not interested	57				
Moved	19				
Other†	94				
Total	254				
Subjects tested		270‡	135	86	49
Excluded from data analysis:		112	35	28	49
Later tooth discordant	36				
Not discharged from nursery with mother, possible head injury, reported to have plumbism or bilingual home	76				
Total	112				
Cases scored and data analyzed		158	100	58	--

*Teachers' behavioral assessment available on 235.

†Infant at home, two working parents, etc.

‡Teachers' behavioral assessment available on 253.

Source: Needleman et al. (1979)

Mean dentine lead values for the 100 children included in the low-Pb and 58 in the high-Pb exposure groups were not reported by Needleman et al. (1979). However, Bellinger and Needleman (1983), who studied 141 of the 158 subjects of Needleman et al. (1979), reported those subjects to have mean dentine Pb levels of 6.2 ppm and 31.4 ppm, respectively. Mean blood Pb levels reported as having been assayed 4-5 years earlier for approximately 50% of the children in these two groups were 23.8 ± 6.0 μg/dℓ vs. 35.5 ± 10.1 μg/dℓ, respectively;

the highest blood-Pb level recorded was 54 μg/dℓ. The low-Pb and high-Pb group children underwent a comprehensive neuropsychologic evaluation, beginning with the Wechsler Intelligence Scale for Children-Revised (WISC-R), with the examiners blind to the Pb-exposure status of the children. In addition to the WISC-R, the children were administered, in set sequence, tests of: concrete operational intelligence; academic achievement (in mathematics, reading recognition, and reading comprehension); auditory and language processing; visual-motor reflexes; attentional performance; and motor coordination. While each child was being tested, the parents filled out a comprehensive medical and social history, received a 58-item questionnaire on parent attitudes, and took the Peabody Picture Vocabulary Test (PPVT). Also, 39 non-lead variables potentially affecting the children's development were scaled and coded, e.g., estimation of parental socioeconomic status (SES) by a two-factor Hollingshead index.

The scores of the high-Pb and low-Pb children for each of 39 control variables were compared statistically by the Student t-Test, with the two groups differing significantly on such variables as age, father's social class and father's education. Scores from the neuropsychologic evaluations of the high-Pb and low-Pb children were then compared statistically, using an analysis of covariance with dentine-Pb level as the main independent variable and with the following five covariates: father's SES (composed of education and occupation score); mother's age at subject's birth; number of pregnancies; mother's education; and parental IQ score. With the exception of these variables and age, the low-Pb and high-Pb groups were similar in regard to most of the non-Pb control factors.

Results of the neuropsychologic evaluations for the low-Pb and high-Pb groups can be summarized as follows: children in the high-Pb group were reported to have performed significantly less well on the WISC-R (especially on the verbal items), on three measures of auditory and visual processing, on attentional performance as measured by reaction time under varying delay conditions, and on most items of the teachers' behavioral ratings. The high-Pb children appeared to be particularly less competent in areas of verbal performance and auditory processing, having obtained lower scores, for example, on tasks requiring: response to verbal instructions of increasing complexity, immediate repetition of previously uttered sentences of increasing complexity, and discrimination of tone sequences of increasing complexity as either alike or different. Impaired focusing of attention (or distraction) of high-Pb children was also reflected by a significantly higher percentage of high-Pb children rating items being found to be significantly different (i.e., more negative) for high-Pb than low-Pb children at $p < 0.05$. Overall, the sum score (mean) of ratings of classroom behavior were found to be significantly poorer for the high-Pb children based on an analysis of covariance.

Burchfiel et al. (1980), using computer-assisted spectral analysis of recordings from a standard EEG examination on 41 (22 low-Pb and 19 high-Pb) children from the Needleman et al.

(1979) study, reported significant increases in percentages of low frequency delta activity and decreases in percentages of alpha activity in the spontaneous EEG of the high-Pb children. Percentages of alpha and delta frequency EEG activity and results for several psychometric and behavioral testing variables (e.g., WISC-R full-scale IQ and verbal IQ, reaction time under varying delay, etc.) obtained for the same children were then employed as input variables (or "features") in direct and stepwise discriminant analyses. The separation determined by these analyses for combined psychological and EEG variables ($p<0.005$) was strikingly better than the separation of low-Pb from high-Pb children using either psychological ($p<0.041$) or EEG ($p<0.079$) variables alone.

A more recent paper by Needleman (1982) provided a summary overview of findings from the Needleman et al. (1979) study and findings reported by Burchfiel et al. (1980) concerning EEG patterns for a small subset of the children included in the 1979 study. Needleman (1982) also summarized results of an additional analysis of the Needleman et al. (1979) data reported elsewhere by Needleman et al. (1982). More specifically, cumulative frequency distributions of verbal IQ scores for the low-Pb and high-Pb subjects from the 1979 study were reported by Needleman et al. (1982) and reprinted as Figure 2 of the Needleman (1982) paper, as shown below in Figure 2. One key point made by Needleman (1982) was that the average IQ deficit of four points demonstrated by the Needleman et al. (1979) study reflected not just further impairment of cognitive abilities of children with already low IQs but rather a shift downward in the entire distribution of IQ scores across all IQ levels in the high-Pb group, with none of the children in that group having verbal IQs over 125.

The Bellinger and Needleman (1983) paper provided still further follow-up analyses of the Needleman et al. (1979) data set, focusing mainly on comparison of the low-Pb and high-Pb children's observed IQs versus their expected IQs based on their mothers' IQs. Bellinger and Needleman reported that regression analyses showed that the IQs of children with elevated levels of dentine Pb (>20 ppm) fell below those expected based on their mothers' IQs and that the amount by which a child's IQ falls below the expected value increases with increasing dentine Pb levels in a nonlinear fashion (see Figure 3 below, showing plots of IQ residuals by dentine Pb levels as illustrated in Figure 2 of the Bellinger and Needleman paper). In fact, examination of the scatterplot shown in Figure 3 and the discussion of results provided by Bellinger and Needleman (1983) indicate that regressions for the 20-29.9 ppm group did not reveal significant associations between increasing Pb levels in that range and IQ residuals, in contrast to statistically significant ($p<0.05$) correlations found between IQ residuals and dentine Pb in the 30-39.9 ppm range.

In order to evaluate critically the above studies, the Committee met with Dr. Needleman at his University of Pittsburgh (Children's Hospital) office facilities in Pittsburgh, PA, on

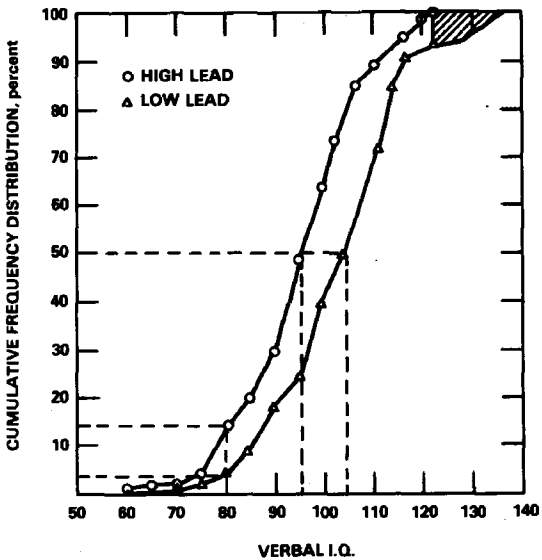

Figure 2. Cumulative frequency distributions of verbal IQ scores in high and low lead subjects.

Source: Needleman (1982) and Needleman et al. (1982).

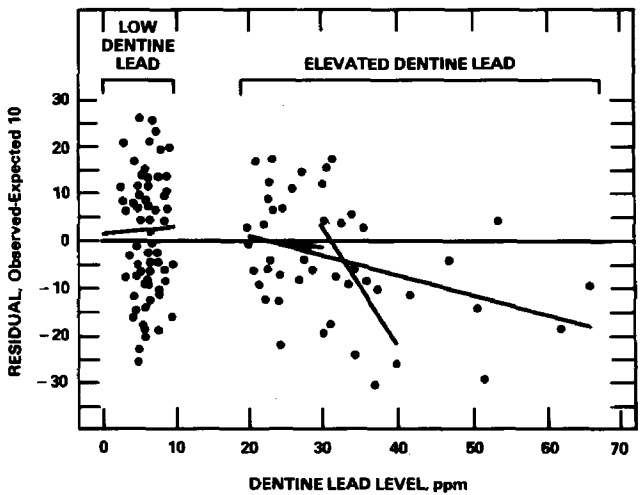

Figure 3. Scatterplot of children's dentine lead level versus residual. Regression lines are shown for four ranges of lead level: low lead, 0.9 to 9.9 ppm; elevated lead, 20.0 to 66.0, 20.0 to 29.9, and 30.0 to 39.9 ppm.

Source: Bellinger and Needleman (1983).

March 30-31, 1983. During that meeting, Dr. Needleman presented an overview focusing mainly on the objectives, design, data collection and statistical analysis procedures, and findings for the original study reported by Needleman et al. (1979). Dr. Needleman also provided additional information regarding follow-up analyses or extensions of the 1979 study either published in other papers referred to above or expected to be published in the near future. This additional information included comments regarding the conduct of a separate study involving the evaluation of teachers' ratings of classroom behavior of children in Lowell, MA (a different population from the one sampled in the 1979 study). Certain listings of raw data (provided in coded form to protect the privacy of subjects), computer printouts summarizing data entries for statistical analyses or results of such analyses, and miscellaneous other pertinent materials were discussed with Dr. Needleman during the March 30-31 meeting. Additional information was requested by the Committee in order to clarify factual points or to help resolve evaluative issues arising from the discussions in March with Dr. Needleman. A portion of the information was provided during the 2-3 months following the March meeting. (See Attachment 1 for a list of materials examined by the Committee in connection with the review of the subject studies.) The Committee's comments regarding the most salient points of concern and controversy related to methodological and other features of the above studies by Needleman and colleagues are presented below.

B. Comments on Needleman et al. (1979) Study

1. Indicators of Exposure

In the principal study (Needleman et al., 1979) as well as in subsequent reports on subsets of subjects from the initial population (e.g., Burchfiel et al., 1980; Bellinger and Needleman, 1983), Pb exposure in the pediatric subjects was assessed by analysis of Pb in the dentine of deciduous teeth. In contrast to blood Pb, which is an exposure marker for relatively recent exposure, whole-tooth or tooth-region analysis for Pb content yields an index of cumulative Pb exposure of the subject up to the time of exfoliation.

In the report of Needleman et al. (1979), blood Pb levels as an additional index of prior exposure were reported as only being available for some (approximately 50%) of the subjects in the highest/lowest deciles, and were discussed only in terms of group means. These measurements were reported to have been obtained as part of a blood screening program in the subject communities 4-5 years prior to collection of tooth samples.

Observations and comments concerning specific aspects of the Pb exposure indices and associated methodological procedures include:

(a) Dentine was isolated from each tooth sample by a procedure described in an earlier report in which the present principal investigator (Dr. Needleman) was also heavily involved (Shapiro et al., 1973). In that procedure, very thin sections of tooth were carefully cut from the central sagittal plane, dentine (coronal plus secondary) was mechanically separated from enamel and circumpulpal dentine, and the dentine samples were dissolved in acid and subsequently analyzed by anodic stripping voltammetry (ASV) for Pb content.

(b) According to Dr. Needleman, the type of tooth selected for analysis was fairly consistent: mainly the incisor, and some bicuspids. Hence, it appears that any variation in Pb content which might arise from random selection of diverse types of dentition (due to variation in Pb content across different types of teeth) would have been minimal.

(c) Unlike blood Pb, there is no external quality control framework by which to evaluate the dentine Pb analyses such as were done in the subject studies. One must therefore consider the specific steps in the analysis against a general body of information. Two steps in the dentine Pb measurement need to be considered. According to Needleman, the homogeneity of dentine in terms of Pb content for a given tooth can vary sufficiently that tooth sectioning was confined to an initial central sagittal sectioning in all cases, the sectioned sample providing two (replicate) samples for analysis. Once dentine was isolated, its subsequent analysis by ASV would be expected to be achieved with good accuracy and precision, given available data for overall performance of ASV assays of Pb in biological matrices and the fact that such Pb levels are relatively high. Since the major determinant of variance in the replicate (single tooth)/duplicate (multiple teeth) analyses was the dentine isolation step, Needleman et al. (1979) attempted to minimize unacceptable variance by use of intra-sample concordance criteria in analyzing relationships between dentine Pb levels and the results of the psychometric test battery.

(d) The impression gained from close reading of the Needleman and other reports, as well as discussions with Needleman, is that use of dentine Pb values entails methodological skill at the step of dentine isolation. From the information available to the Committee as to actual variation in dentine Pb across a given tooth sample, it appears that ±15% represents a reasonable specific estimate of variability for the dentine analysis for subjects from the low-Pb and high-Pb groups included in statistical analyses of neuropsychologic test outcomes

(i.e., for subjects with the greatest concordance among their dentine Pb values). Much greater variation existed among replicate or duplicate dentine Pb values for individuals from the low-Pb and high-Pb groups excluded from the statistical analyses. Examination of replicate/duplicate values for measurements for all subjects in the study (including the 2000+ students for which teachers' ratings were obtained) would be necessary to determine an overall estimate of variance for dentine Pb measurements in the study.

(e) Whole-tooth analysis would be simpler technically and has been more often employed than specific tooth-region analysis. However, one can also expect that such a measure would be less sensitive as a biological index of Pb exposure due to the inclusion of enamel, a region that contributes significiantly to tooth mass but has relatively invariant low Pb content regardless of exposure. In the case of whole-tooth Pb, it is known that Pb content is linearly related to age of the subject and that the values of the slopes of Pb content vs. age are better indicators of Pb exposure than just the Pb concentrations alone (Steenhout and Pourtois, 1981). Shapiro and coworkers (1978) have also reported that there is a better correlation of tooth Pb concentration/year with either blood Pb or erythrocyte porphyrin than just Pb concentration unadjusted for age. Expression of dentine Pb as a function of age in the present study ($\mu g\ Pb \cdot g\ dentine^{-1} \cdot yr^{-1}$) would be desirable, especially because the mean age of the high-Pb subjects was greater than that of the low exposure group. While this method of expressing Pb exposure would have minimal effect on the categorization of subjects into high- and low-Pb groups, it might be expected to influence relationships between Pb and other variables, e.g., in Figure 3 (above) from Bellinger and Needleman (1983).

(f) The relative quality of the earlier blood Pb determinations for some low-Pb and high-Pb subjects cannot be ascertained and must be considered more suspect than the main exposure measure used (i.e., dentine Pb). At the time blood Pb levels were measured in the subjects, the quality control for the community Pb-screening programs was minimal, with sampling being done by finger puncture and transfer to capillary tube (communication of V. N. Houk to H. L. Needleman, see Needleman, November 22, 1982: letter to L. D. Grant). These limitations on the relative reliability of such measurements apparently were the reason for Dr. Needleman's discussion of these values only in terms of group means for the low-Pb and high-Pb subjects. Given present knowledge about the impact of sampling protocols on the accuracy of blood Pb measurements, one can reasonably say that finger puncture plus capillary tube versus venous puncture plus low-Pb

blood tube would impart a significant positive bias to the blood Pb levels obtained. Hence, the overall means reported for the low-Pb and high-Pb groups in terms of blood Pb would, if anything, likely be higher than their true values for the 50% of the low-Pb and high-Pb children sampled.

(g) Apart from the issue of reliability of the blood Pb measures under consideration is the question of age of the children at the time of blood sampling relative to the known variation of blood Pb with age in children for a given exposure setting: i.e., blood Pb levels in children generally tend to peak at 2-3 years of age and decline in subsequent years. Available information on the ages of the children at the time of psychometric testing, the years when such testing occurred, and the years when blood Pb measurements were made indicate that the ages of some children at the time of blood Pb measurement were probably at or not materially beyond the period of typical peaking in blood Pb, but others may have been sampled at a later age within 1-2 years (during 1973-74) prior to their participation in neuropsychologic testing while in first or second grade (as early as during 1975-76). It would be necessary to know the ages of specific subjects when the blood lead determinations were done and their age at neuropsychologic testing before reliable judgments could be made regarding the representativeness of the reported mean blood Pb values for either the low-Pb or high-Pb subjects.

2. Psychometric Measurements and Procedures

The study employed a comprehensive neuropsychological battery to assess the children's behavioral functioning. The measures included the WISC-R, Piagetian tasks, and selected tests of academic achievement, auditory and language processing, visual and motor performance, reaction time, motor coordination, and teacher ratings of classroom behavior. Mothers' attitudes toward child rearing and parental IQ (indexed by the PPVT) were also assessed. The PPVT is a narrow assessment of mothers' intelligence, but their PPVT scores correlated in expected ways with other variables in the study.

Dr. Needleman administered the PPVT to the mothers, and three other examiners administered the WISC-R and other assessments of the children in a fixed order. The examiners were blind as to children's Pb levels and scored the test immediately after the test session. It is not known how qualified the examiners were to administer individual tests, but Dr. Needleman reported that the examiners were instructed on how to administer and score the test.

In a recent publication (Needleman, 1983, p. 243) additional details of the psychometric procedures were reported. Children with low-Pb exposure were scheduled early in the study,

because "I wanted my technicians to get some experience with normal children." In addition, Dr. Needleman told the Committee during the meeting in Pittsburgh that the study began with three technicians, one of whom left during the study and was replaced by a fourth tester. Results of the Needleman et al. (1979) and related publications using the psychometric test scores could be affected by this nonrandom ordering of assessments.

Dr. Needleman reported that quality assurance procedures for ensuring the accuracy of teachers' ratings and neuropsychologic test results used in statistical analyses included: (1) summing of teacher ratings across items and entry of scores for each item and sum scores onto computer cards, followed by verification and transfer onto magnetic tapes; (2) checking of neuropsychologic test scores by a second examiner other than the one doing the original scoring, followed by entry onto cards, verification, and transfer to magnetic tapes; (3) subsequent 5% sampling of computer tape entries to check accuracy against original data listings, with 12 errors in 15,600 columns of entries being found and corrected.

The Committee's inspection of raw data during the March visit with Dr. Needleman revealed some problems of another kind, however. Printouts of parental IQ data for low- and high-Pb subjects included in the statistical analyses (e.g., analyses of covariance) published in the 1979 article revealed errors in calculating parental IQ values for some subjects when their fathers and mothers were both administered the Peabody Picture Vocabulary Test. Instead of an average of mothers' and fathers' scores (midparent IQ), the parents' IQ scores were evidently combined by taking one-half of one parent's score and adding that value to the other parent's score. This erroneous procedure resulted in some parental IQ values that lie well outside probable values. These errors were confirmed later by Dr. Needleman in his letter of October 4, 1983 to Dr. Bernard Goldstein. The impact of this is to introduce error into the results of all of the published analyses of the data set where parental IQ was included as a variable. Correcting these errors would alter the results of the analyses. The precise influence of the errors on the results can be determined only by reanalyzing the data, and the Committee urges that this be done.

During inspection of raw data, the Committee also noted a seemingly higher proportion of large discrepancies between the children's WISC-R Verbal and Performance Scale IQ scores than would be expected in an unselected sample. The discrepancies seemed to be distributed across the high-Pb and low-Pb groups. Neither sufficient time nor facilities were available during the data inspection to carry out an adequate quantitative analysis of the relationship of the verbal to performance IQs, but if the discrepancies are as large and/or numerous as they appeared to be, this may raise questions about the validity of the WISC-R assessment as employed in this study.

3. Statistical Analyses

Comments on specific aspects of the statistical analyses employed in the Needleman et al. (1979) study include the following:

(a) The statistical analyses for teachers' rating scores for classroom behavior were based on classification of the children's Pb exposure levels in terms of first dentine lead values obtained for the first tooth submitted by each of the 2146 subjects included in the analyses (vide supra). Six lead exposure categories were defined as indicated in Figure 1 (i.e., <5.1, 5.1-8.1, 8.2-11.8, 11.9-17.1, 17.2-27.0, and >27.0 ppm dentine Pb), with group boundaries chosen to give symmetrical cell sizes around the median (i.e., 6.8% in Groups 1 and 6, 17.6% in Groups 2 and 5, and 25.6% in Group 4, respectively). However, no statistical analyses that take into account other potentially confounding variables were done on the teachers' rating data shown in Figure 1 and, thus, the dose-response relationships shown in that figure cannot be attributed to Pb exposure alone.

In addition, questions arise regarding the appropriateness or accuracy of classification of subjects in terms of the narrow dentine Pb ranges employed in plotting the dose-response data shown in Figure 1. Given the 15% variability noted for replicate analyses of teeth for those subjects with the most highly concordant dentine Pb values, many subjects who were included in one or another of the six exposure categories based on first dentine Pb analyses could be more appropriately classified as belonging in a different exposure category, according to later replicate/duplicate dentine Pb values. This is particularly likely if the same or analogous concordance criteria used by Dr. Needleman to select low-Pb and high-Pb subjects for inclusion in statistical analyses of later psychometric test scores were used for the teachers' rating analyses. Inspection of raw dentine Pb values for subjects provisionally classified as low-Pb or high-Pb subjects for psychometric testing, but then excluded from final statistical analyses of the psychometric test results because of non-concordance of dentine Pb values, revealed that shifts across the six exposure categories could be substantial if replicate or duplicate dentine Pb values beyond the first dentine Pb value were taken into account.

(b) In regard to the statistical analysis of results from the subsequent psychometric testing phase of the study, comparisions were made only between those

children reported to be ranked in the highest 10th percentile for dentine Pb concentrations and those in the lowest 10th percentile. This strategy certainly maximizes the chances for finding significant differences. Reviewing Figure 1 of the 1979 report, the Committee notes that a group with "moderate" exposure might serve to provide evidence for a dose-response relationship (which, if found, would argue more strongly in favor of a causal connection than the polar low-Pb vs. high-Pb group comparision used). An earlier report on the subject (Needleman, 1977) suggests an intention to use low, medium, and high dentine Pb groups, and a very recent report (Needleman, 1983; Table 6; p. 237) does show some results on behavior ratings for a group of 13 subjects with "middle" dentine Pb levels. Psychological test scores have evidently been obtained for a middle group of subjects (Needleman, 1983, p. 242). The Committee recommends that analyses be undertaken to evaluate any available psychometric testing data for "intermediate" lead-exposure subjects.

(c) Many questions about sampling procedures arise from the exclusion of large numbers of potential participants in the psychometric testing phase of this study. From 542 provisionally eligible participants, almost half were excluded from neuropsychological assessment, and 41 percent of those tested were later excluded from data analyses. Although reasons for the exclusions were given (see Table 1 of the 1979 article), the distribution of demographic and psychological outcome measures for those excluded from the low- and high-Pb groups was provided neither in the published article nor by the investigator to the Committee. The Committee could not fully evaluate sources of possible bias due to such exclusions in the selection of the sample reported in this paper and other publications reviewed.

Some of the criteria used to define Pb exposure levels or to exclude subjects from statistical analyses seemed arbitrary, and different results might have been obtained with application of equally good or better alternative criteria for classification of Pb exposure levels and groups. For example, some subjects provisionally classified as low-Pb or high-Pb subjects based on initial dentine Pb values were excluded from final data analyses based on discordances arising from later replicate or duplicate Pb values obtained for the same or different teeth, although certain key "discordant" dentine Pb values were not meaningfully different from the cut-off criteria levels for inclusion as low-Pb or high-Pb subjects. Thus, exclusion of some subjects from the low-Pb group for statistical analyses hinged on a single dentine Pb value (e.g., 10.1

or 10.5 ppm) barely exceeding the 10 ppm criterion ultimately selected and rigidly enforced as defining the low-Pb (or lowest decile) exposure group, although such dentine Pb values were as likely to have true readings below 10 ppm as were certain key values (e.g., 9.5 or 9.8 ppm) for some subjects included in the low-Pb group likely to have true readings above 10 ppm. Also, since inclusion or exclusion of subjects in the statistical analyses was based on dentine Pb values for all teeth submitted by a given subject over the course of the study, some subjects may have been classified as high-Pb or low-Pb children (or excluded from analysis) based on replicate or duplicate dentine Pb values obtained for teeth shed up to 1-3 years after their psychometric testing. The impact of this may not have been symmetrically exerted on the high-Pb and low-Pb groups. That is, it is not likely that "actual" high-Pb exposure children at the time of psychometric testing would have distinctly lower later dentine Pb values; but low-Pb children with initial values <10 ppm could have experienced lead exposures after psychometric testing that substantially increased their later dentine Pb values and resulted in their exclusion from the low-Pb group.

(d) Normalized outcomes for which age-normed scores were not available were constructed by regressing on age before analysis of covariance. Assuming that age effects were accounted for, five covariates (namely, mother's age at subject's birth, mother's educational level, father's socioeconomic status, number of pregnancies, and parental IQ) were considered. Only five covariates were used because that is the limit dictated by a widely used computer software package (SPSS). However, the number of covariates considered should not be arbitrarily dictated by the constraints of a packaged program but should be determined with the goal of properly controlling confounding variables. Father's education (grade) level was not included separately, although (as Dr. Needleman argued) it is part of father's socioeconomic status. It would seem to be better, based on the results shown in Table 5 of the 1979 report, to use father's education directly rather than as part of a diluted "socioeconomic status" variable.

(e) The Committee reviewed computer printouts from numerous SPSS analysis of covariance runs on psychometric testing data indicated by Dr. Needleman as forming the basis for the results and conclusions presented in the 1979 report and noticed many missing data points among the analyses. In fact, the actual number of data points used in certain regression analyses was sometimes as much as 20%

fewer than those for the 158 cases claimed in the 1979 paper to have been analyzed for the low-Pb and high-Pb subjects. For example, the analyses later reported in the Bellinger and Needleman (1983) paper (on the same data set discussed in the 1979 article) are based on 17 fewer cases than the 158 stated to have been included in the final statistical analyses of psychometric test results appearing in the 1979 article, because of missing parental IQ data for the 17 cases. Missing data, not alluded to in the 1979 report, can pose a serious validity problem if the missing observations are not randomly distributed across the important variables. The effects of such missing data are impossible to assess without detailed analysis of the available data set.

(f) Based upon cursory inspection of the numerous statistical analysis computer runs provided by Dr. Needleman (which was all that was possible during the limited time of access to the printouts), the Committee came away with the impression that most runs led to non-significant findings. In a recent publication (Needleman, 1983), the investigator notes that of the 66 outcomes evaluated, 15 were significantly different between the low- and high-lead groups, given the control variables included in the analyses. He notes that 1 in 20 would be expected by chance, if the outcome variables were uncorrelated. Of course, most of the psychological assessments in this study are moderately to highly correlated, so that this probability does not apply. In addition, apparent group differences are affected by the method of handling important covariates.

(g) Of special interest, printouts for several regression analyses in which child's age was entered as a control variable showed reduced and generally non-significant coefficients for Pb levels, but such findings are not presented in the 1979 report or later articles by Needleman and colleagues. This is in contrast to the earlier reporting (Needleman et al., 1978) of statistically significant Pb effects when age was included as a covariate in preliminary statistical analyses performed when the collection of psychometric data for the study was about one-half completed. The standardized psychometric measures with age norms provided do not perfectly correct for age differences in a specific sample. Because there are significant age differences between the high-Pb and low-Pb groups in this study, the regressions of raw test scores on child's own age would have been the more desirable analyses to report. The Committee has reached this conclusion despite the principal investigator's (Dr. Needleman's) argument that it is undesirable to "correct for age twice."

4. Committee Conclusions and Recommendations

Estimation of Pb exposures by dentine Pb measurements is more appropriate than blood Pb as an index of cumulative exposure, and the analytical determination of such dentine Pb levels appears to have generally been done competently in the study. However, it is not possible to estimate the variance of the dentine Pb measurements in replicate/duplicate analyses (beyond the 15% estimate arrived at for replicate analyses for the most concordant samples) without full access to the coded, raw data of all children who participated in the study. The blood Pb measurements, obtained earlier for some of the children, are of unknown reliability. Because the blood data appear to have been obtained at varying ages for the children sampled, the reported blood Pb data probably do not uniformly assess peak exposure levels for them and cannot be accepted as providing quantitive estimates of Pb levels associated with any neurobehavioral deficits demonstrated to exist among the children studied.

Teacher ratings of children's classroom behaviors were collected on more than 2000 children who also contributed shed deciduous teeth for dentine Pb analyses. The failure to revise the lead classification of the children based on discrepancies with later replicate/duplicate dentine Pb values in the analysis of teachers' ratings contrasts sharply with the demand for concordance of dentine Pb readings in the neuropsychological testing phase of the study. Also, the failure to analyze for possible contributions of confounding factors or covariates to the teachers' rating results is disturbing. (The covariance adjustment used for teachers' ratings on the 158 children included in the neuropsychological testing phase of the study is subject to the criticisms noted for other analyses of data for those groups.) The dose-response relationships reported to exist between dentine Pb levels and teachers' rating scores, therefore, cannot be accepted as valid based on the published analyses.

A comprehensive neuropsychological test battery was administered to the children defined as belonging in low-Pb or high-Pb subgroups. Serious questions exist regarding the basis for classification of subjects in these groups or exclusion of others from them. Also, discrepancies between WISC-R verbal and performance scores, if as large or numerous as they seem upon cursory inspection, may raise questions about the test administration or the sample selection. Errors in the calculation of some averaged parental IQ scores, evident in coded materials provided to the Committee, introduced unknown errors into the regression analyses for the psychometric testing results. The use of the PPVT for parental IQ was not ideal, but was still acceptable. Exclusion of large numbers of eligible participants prior to data analysis could have resulted in systematic bias in the results. However, the Committee was unable to evaluate this possibility fully, given the limited information made available by the investigator.

The treatment of covariates in the statistical analysis of the psychometric testing results was unsatisfactory. The failure to report statistical analyses showing generally reduced or non-significant negative correlations between dentine Pb levels and performance on the psychometric tests also lessens the credibility of those few statistically significant effects attributed to Pb in the published version(s) of the Needleman et al. (1979) study.

In summary, at this time, based on the questionable Pb exposure categorization and subject exclusion methods, problems with missing data, and concerns regarding the statistical analyses employed and selected for reporting, the Committee concludes that the study results, as reported in the Needleman et al. (1979) paper, neither support nor refute the hypothesis that low or moderate levels of Pb exposure lead to cognitive or other behavioral impairments in children. The Committee strongly recommends that the subject data set be reanalyzed to correct for errors in data calculation and entry noted above, that the reanalysis be based on better exposure classification of subjects, and that all potentially confounding variables (including age) be assessed using a backwards elimination approach analogous to that recommended earlier for the reanalysis of Ernhart data.

C. Comments on the Burchfiel et al. (1980) Study

The Committee carried out only a very preliminary review of the Burchfiel et al. (1980) study, focusing mainly on consideration of Pb exposure, neuropsychologic testing, and statistical analysis aspects of the study. Review of the electrophysiological recording aspects of the study would require additional committee members or a separate review committee with recognized expertise in electrophysiology and, in particular, electroencephalography.

In view of the fact that the Pb exposure and psychometric measurement data utilized in the Burchfiel study are subsets of the data underlying the Needleman et al. (1979) article discussed above, most of the preceding comments regarding those aspects apply here as well. Only a few additional remarks are, therefore, felt to be necessary here. Specifically, no definite dentine Pb or blood Pb values were reported for the specific children from the Needleman et al. (1979) study who underwent the EEG evaluations reported by Burchfiel et al. (1980). It is therefore impossible to determine with any confidence the specific Pb exposure levels (including either blood Pb or dentine Pb values) that may have been associated with the reported EEG effects. Nor is it possible to accept with much confidence any reported relationships between the observed brain wave alterations, the psychometric testing scores, and Pb exposure classification as low-Pb or high-Pb, especially in view of the various problems noted above regarding exposure classification, psychometric testing, and statistical treatment of covariates or confounders that preclude acceptance of the findings reported in the 1979 publication.

D. Comments on the Needleman (1982) Report

The 1982 report published by Needleman represents mainly a summary or restatement of findings already reported in the earlier Needleman et al. (1979), Burchfiel et al. (1980), and Needleman et al. (1982) publications. The comments provided above on the first two of the earlier publications, obviously, also apply here.

One additional point worthy of discussion concerns the plot of cumulative frequency distributions of verbal IQ scores for low-Pb and high-Pb subjects shown in Figure 2 of the Needleman (1982) report, as reprinted from the Needleman et al. (1982) article. Given the serious reservations expressed earlier by the Committee regarding the Pb-exposure classification procedures, aspects of the psychometric testing, and statistical treatment of covariates or confounding factors as employed in the analyses reported in the 1979 article, the particular cumulative distribution curves shown in the figure for verbal IQ scores among the low-Pb and high-Pb subjects cannot be accepted at this time as being either qualitatively valid (i.e., as demonstrating lower IQs for high-Pb subjects than for low-Pb subjects) or quantitatively accurate (i.e., in terms of absolute decreases in IQ implied to be associated with Pb exposure). Similarly, the Committee finds certain statements in the discussion (page 731 of the 1982 Needleman paper) of the cumulative distribution curves to be somewhat misleading in noting that none of the included high-Pb subjects had an IQ over 125 (while 5% of the low-Pb subjects did) but failing to mention that at least one subject excluded because of overt plumbism had a full-scale WISC-R IQ over 125.

E. Comments on the Bellinger & Needleman (1983) Study

This paper reports two kinds of reanalyses of the data from the previous (Needleman et al., 1979) report and, again, most of the comments made earlier on aspects of that study also apply here. Certain additional comments are warranted, however. First, child IQ is regressed on mother's IQ separately for the low-Pb and high-Pb groups. The results are that mother-child IQ correlations do not differ for the two Pb exposure groups and the high-Pb group has lower than predicted IQ scores (controlling for maternal IQ).

Second, the residuals of child's IQ regressed on mother's IQ from the first analysis were regressed on dentine Pb levels, arranged by individual values. Four ranges of lead values were used to estimate regression slopes of residual IQ on lead. The sample size for the low-Pb group in this report was N=94; for high-Pb, N=47; and for two subsamples of the high-Pb group, i.e., dentine Pb levels of 20.0-29.9 ppm, N=24, and for 30.0-39.9 ppm, N=17. The

latter two groups are far too small to be used to estimate slopes that can be credibly generalized to other samples. The results for the regression of child's IQ residuals on lead in the low-Pb group had, not surprisingly, a slope of zero because of extreme restriction of the range of lead values. The slope for the high-Pb group was -0.36, significantly different from zero. One serious problem in interpreting these results is that only maternal IQ was used as a "covariate" for child IQ. No other background factors, as reported in the earlier paper, were included as adjustments for the residualized IQ scores in this study.

To control, in part, for additional covariates that could affect the relationships between residual IQ and lead level, a stepwise regression was done. Surprisingly, and contrary to all of their other analyses of these data, lead level was allowed to enter the equation second, before two of the three control variables. Table III of the Bellinger and Needleman (1983) article reported results in the form of unstandardized regression coefficients without accompanying standard errors or significance levels. The F ratios reported seemed to be those of the equations, not of the individual coefficients, except of course for the first variable in the first step. Thus, it is not clear that the Pb coefficient is actually reliably different from zero.

Given the above problems and concerns, the reanalyses of the Needleman data set presented in the Bellinger and Needleman (1983) paper cannot be accepted as providing credible or reliable estimates of quantitative relationships between Pb exposure and neuropsychologic deficits in children. Nor can the reported results be taken as either qualitatively supporting or refuting the hypothesis of associations between low-level lead exposure and cognitive deficits in children.

F. Comments on the Needleman (1981) Report

Shed teeth and teacher ratings were collected in 1977-1978 from a new sample of about 1300 first-grade children in Lowell, MA. Children were classified into five groups according to their dentine Pb levels: Group 1, ≤6.4 ppm; Group 2, 6.5 to 8.7 ppm; Group 3, 8.71 to 12 ppm; Group 4, 12.01 to 18.1 ppm; Group 5, ≥18.2 ppm. The association of teacher ratings on 11 behavior scales with Pb levels is displayed separately for males and females in Figures 4 and 5. No effort was made to control for confounding variables in this overall set of results.

Essentially complete follow-up data and Pb levels were obtained on 130 children of the 447 males selected for follow-up. Given the design of this study, the expected analysis would investigate the relationship between teacher ratings and Pb level following adjustment for confounding variables, collected on the follow-up sample. Such an analysis was not reported.

In the Committee's view, these data should be reanalyzed to show clearly the form of the relationship between Pb level and teacher ratings, with appropriate controls for the follow-up subjects.

POSTSCRIPT

In addition to evaluation of the studies of Ernhart and Needleman, the Committee reviewed available reports (some published and others as yet unpublished) of other studies from the United States and Europe. These studies included, for example, those by: Winneke et al. (1982, 1983), Winneke (1983), Yule et al. (1981), Lansdown et al. (1983), Smith (1983), and Harvey et al. (1983). Although an exhaustive, in-depth evaluation of the world literature on low-level Pb exposure was beyond the current charge to the Committee, we note that new studies reported in the spring and summer of 1983, with only a few exceptions, failed to find significant association between low-level Pb exposure and neuropsychologic deficits, once control variables were taken into account.

From its review of the recent research literature covered in this report, the Committee concludes that: (1) in the absence of control for other variables, a negative association between Pb exposure and neuropsychologic functioning has been established; (2) the extent of this negative association is reduced or eliminated when confounding factors are appropriately controlled; and (3) the Committee knows of no studies that, to date, have validly established (after proper control for confounding variables) a relationship between low-level Pb exposure and neuropsychologic deficits in children.

Research addressing possible dose-response relationships between lead and cognitive functioning in children is a worthy effort, and the Committee hopes that future studies can gather data that speak more adequately to this issue. In the view of the Committee, it is unlikely that continued use of cross-sectional epidemiological analyses will produce much credible evidence for or against the hypothesis that low to moderate levels of lead exposure are responsible for neurobehavioral deficits in apparently asymptomatic children. The study design generally does not allow for unambiguous disentangling of possible contributions of such lead exposures to observed cognitive or behavioral deficits versus the contributions of numerous other potentially confounding factors. There is a great need for longitudinal and time-series analyses, which include detailed prospective measurements of Pb exposure indices from early childhood onward and repeated sampling of neurobehavioral endpoints, both during preschool and school-age years.

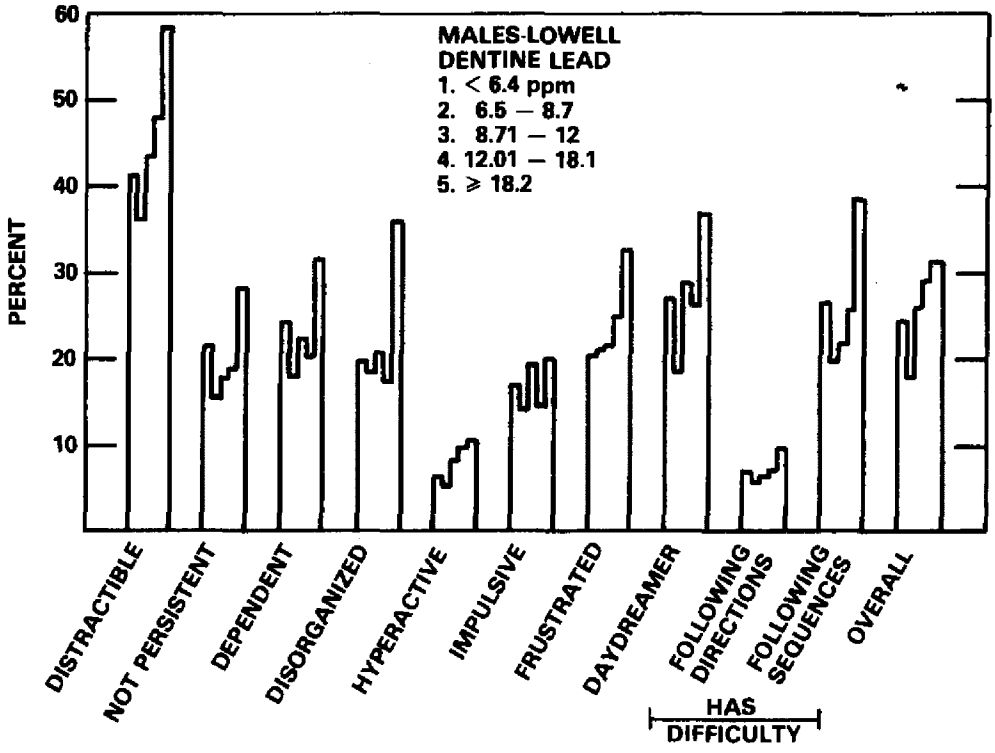

Figure 4. The relationship between negative teachers' ratings and dentine lead level in males. Each sample was classified into 5 groups according to dentine lead level. Each item was then scored. Within each item, Group 1, lowest lead level, is at the left; Group 5, highest lead level, is at the right.

Source: Needleman (1981).

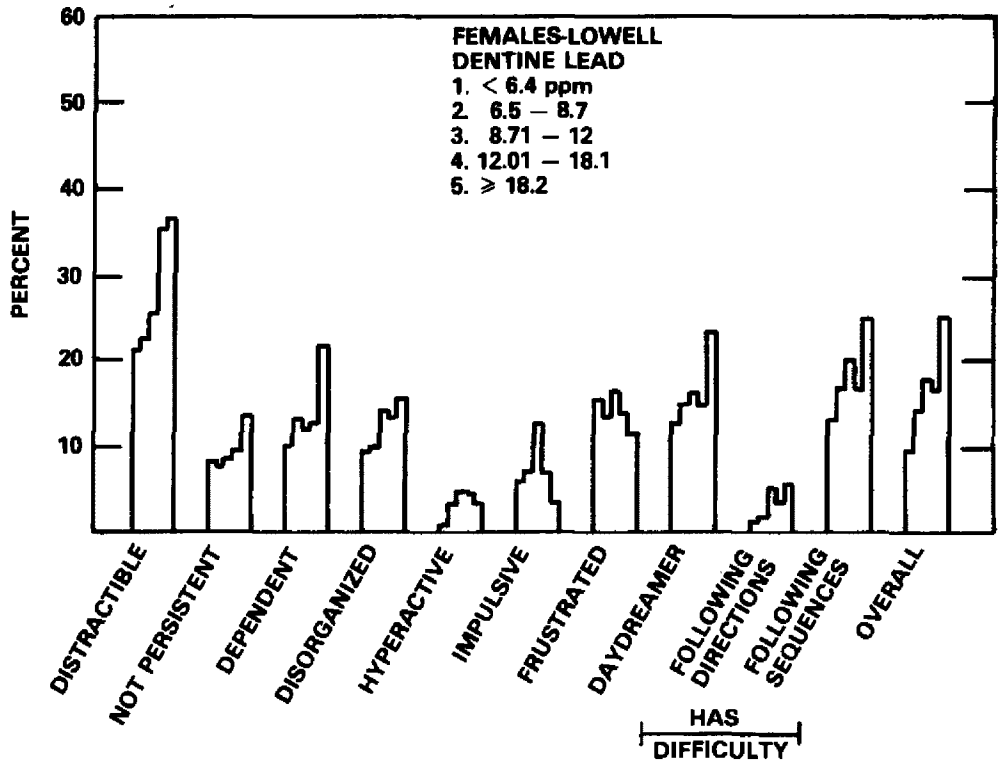

Figure 5. The relationship between negative teachers' ratings and dentine lead level in females. Each sample was classified into 5 groups according to dentine lead level. Each item was then scored. Within each item, Group 1, lowest lead level, is at the left; Group 5, highest lead level, is at the right.

Source: Needleman (1981).

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ATTACHMENT 1

Additional materials considered in review of studies by Dr. Claire Ernhart and colleagues

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22. Needleman, H. L. (1983) Listings of coded raw data for psychometric test results and background variables (e.g., sex, age, father's education, parental I.Q., etc.) for "included" and "excluded" subjects in Needleman et al. (1979) study. Attachment to Item 20 above.

23. Needleman, H. L. (1983) Computer printouts of frequency distribution of IQ scores and other psychometric test results for high and low lead subjects in Needleman et al. (1979) study. Inspected by Committee at H. L. Needleman's facilities at University of Pittsburgh (Children's Hospital), Pittsburgh, PA.

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Research and Development

EPA

Air Quality Criteria for Lead

Review Draft

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Volume I of IV

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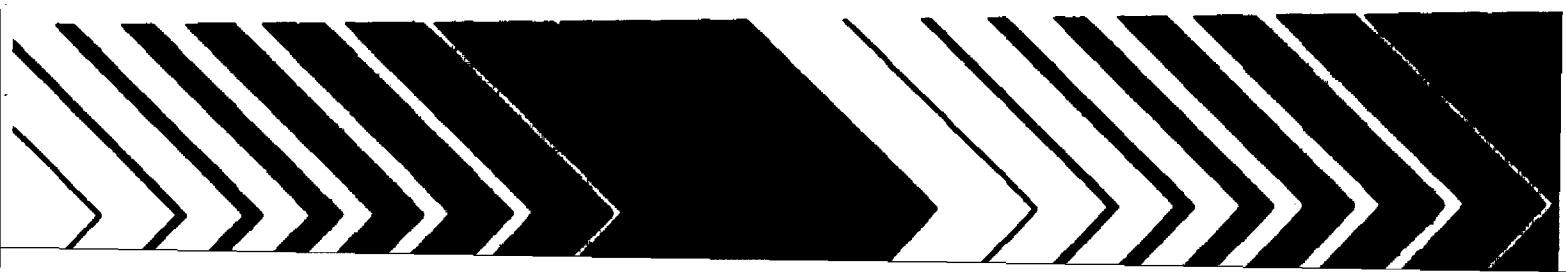

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Example-

Section	Page	Paragraph	Line	Specific Comments
2.2.3	15	2	2	Discussion on ... does not consider studies by ... in making conclusions.
2.2.3	20	3	5	"Susceptible to change" would be more appropriate than "sensitive."

4. When commenting on specific sections/discussion and paragraphs/statements, some suggested reviewer responses that may be useful include (with additional appropriate details by reviewer):

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Air Quality Criteria for Lead

Volume I

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Environmental Criteria and Assessment Office
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ABSTRACT

The document evaluates and assesses scientific information on the health and welfare effects associated with exposure to various concentrations of lead in ambient air. The literature through 1983 has been reviewed thoroughly for information relevant to air quality criteria, although the document is not intended as a complete and detailed review of all literature pertaining to lead. An attempt has been made to identify the major discrepancies in our current knowledge and understanding of the effects of these pollutants.

Although this document is principally concerned with the health and welfare effects of lead, other scientific data are presented and evaluated in order to provide a better understanding of this pollutant in the environment. To this end, the document includes chapters that discuss the chemistry and physics of the pollutant; analytical techniques; sources, and types of emissions; environmental concentrations and exposure levels; atmospheric chemistry and dispersion modeling; effects on vegetation; and respiratory, physiological, toxicological, clinical, and epidemiological aspects of human exposure.

PRELIMINARY DRAFT

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LIST OF ABBREVIATIONS

AAS	Atomic absorption spectrometry
Ach	Acetylcholine
ACTH	Adrenocoticotrophic hormone
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADP/O ratio	Adenosine diphosphate/oxygen ratio
AIDS	Acquired immune deficiency syndrome
AIHA	American Industrial Hygiene Association
AII	Angiotensin II
ALA	Aminolevulinic acid
ALA-D	Aminolevulinic acid dehydrase
ALA-S	Aminolevulinic acid synthetase
ALA-U	Aminolevulinic acid in urine
APDC	Ammonium pyrrolidine-dithiocarbamate
APHA	American Public Health Association
ASTM	Amercian Society for Testing and Materials
ASV	Anodic stripping voltammetry
ATP	Adenosine triphosphate
B-cells	Bone marrow-derived lymphocytes
Ba	Barium
BAL	British anti-Lewisite (AKA dimercaprol)
BAP	benzo(a)pyrene
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
BW	Body weight
C.V.	Coefficient of variation
CaBP	Calcium binding protein
CaEDTA	Calcium ethylenediaminetetraacetate
CBD	Central business district
Cd	Cadmium
CDC	Centers for Disease Control
CEC	Cation exchange capacity
CEH	Center for Environmental Health
CFR	reference method
CMP	Cytidine monophosphate
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CP-U	Urinary coproporphyrin
C_{pah}	plasma clearance of p-aminohippuric acid
Cu	Copper
D.F.	Degrees of freedom
DA	Dopamine
DCMU	[3-(3,4-dichlorophenyl)-1,1-dimethylurea
DDP	Differential pulse polarography
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
EEC	European Economic Community
EEG	Electroencephalogram
EMC	Encephalomyocarditis
EP	Erythrocyte protoporphyrin
EPA	U.S. Environmental Protection Agency

LIST OF ABBREVIATIONS (continued).

FA	Fulvic acid
FDA	Food and Drug Administration
Fe	Iron
FEP	Free erythrocyte protoporphyrin
FY	Fiscal year
G.M.	Grand mean
G-6-PD	Glucose-6-phosphate dehydrogenase
GABA	Gamma-aminobutyric acid
GALT	Gut-associated lymphoid tissue
GC	Gas chromatography
GFR	Glomerular filtration rate
HA	Humic acid
Hg	Mercury
hi-vol	High-volume air sampler
HPLC	High-performance liquid chromatography
i.m.	Intramuscular (method of injection)
i.p.	Intraperitoneally (method of injection)
i.v.	Intravenously (method of injection)
IAA	Indol-3-ylacetic acid
IARC	International Agency for Research on Cancer
ICD	International classification of diseases
ICP	Inductively coupled plasma
IDMS	Isotope dilution mass spectrometry
IF	Interferon
ILE	Isotopic Lead Experiment (Italy)
IRPC	International Radiological Protection Commission
K	Potassium
LAI	Leaf area index
LDH-X	Lactate dehydrogenase isoenzyme x
LC_{50}	Lethyl concentration (50 percent)
LD_{50}	Lethal dose (50 percent)
LH_{50}	Luteinizing hormone
LIPO	Laboratory Improvement Program Office
ln	National logarithm
LPS	Lipopolysaccharide
LRT	Long range transport
mRNA	Messenger ribonucleic acid
ME	Mercaptoethanol
MEPP	Miniature end-plate potential
MES	Maximal electroshock seizure
MeV	Mega-electron volts
MLC	Mixed lymphocyte culture
MMD	Mass median diameter
MMED	Mass median equivalent diameter
Mn	Manganese
MND	Motor neuron disease
MSV	Moloney sarcoma virus
MTD	Maximum tolerated dose
n	Number of subjects
N/A	Not Available

LIST OF ABBREVIATIONS

NA	Not Applicable
NAAQS	National ambient air quality standards
NADB	National Aerometric Data Bank
NAMS	National Air Monitoring Station
NAS	National Academy of Sciences
NASN	National Air Surveillance Network
NBS	National Bureau of Standards
NE	Norepinephrine
NFAN	National Filter Analysis Network
NFR-82	Nutrition Foundation Report of 1982
NHANES II	National Health Assessment and Nutritional Evaluation Survey II
Ni	Nickel
OSHA	Occupational Safety and Health Administration
P	Potassium
p	Significance symbol
PAH	Para-aminohippuric acid
Pb	Lead
PBA	Air lead
$Pb(Ac)_2$	Lead acetate
PbB	concentration of lead in blood
PbBrCl	Lead (II) bromochloride
PBG	Porphobilinogen
PFC	Plaque-forming cells
pH	Measure of acidity
PHA	Phytohemagglutinin
PHZ	Polyacrylamide-hydrous-zirconia
PIXE	Proton-induced X-ray emissions
PMN	Polymorphonuclear leukocytes
PND	Post-natal day
PNS	Peripheral nervous system
ppm	Parts per million
PRA	Plasma renin activity
PRS	Plasma renin substrate
PWM	Pokeweed mitogen
Py-5-N	Pyrimide-5'-nucleotidase
RBC	Red blood cell; erythrocyte
RBF	Renal blood flow
RCR	Respiratory control ratios/rates
redox	Oxidation-reduction potential
RES	Reticuloendothelial system
RLV	Rauscher leukemia virus
RNA	Ribonucleic acid
S-HT	Serotonin
SA-7	Simian adenovirus
scm	Standard cubic meter
S.D.	Standard deviation
SDS	Sodium dodecyl sulfate
S.E.M.	Standard error of the mean
SES	Socioeconomic status
SGOT	Serum glutamic oxaloacetic transaminase

LIST OF ABBREVIATIONS (continued).

sIg	Surface immunoglobulin
SLAMS	State and local air monitoring stations
SMR	Standardized mortality ratio
Sr	Strontium
SRBC	Sheep red blood cells
SRMs	Standard reference materials
STEL	Short-term exposure limit
SW voltage	Slow-wave voltage
T-cells	Thymus-derived lymphocytes
t-tests	Tests of significance
TBL	Tri-n-butyl lead
TEA	Tetraethyl-ammonium
TEL	Tetraethyllead
TIBC	Total iron binding capacity
TML	Tetramethyllead
TMLC	Tetramethyllead chloride
TSH	Thyroid-stimulating hormone
TSP	Total suspended particulate
U.K.	United Kingdom
UMP	Uridine monophosphate
USPHS	U.S. Public Health Service
VA	Veterans Administration
V_d	Deposition velocity
VER	Visual evoked response
WHO	World Health Organization
XRF	X-Ray fluorescence
X^2	Chi squared
Zn	Zinc
ZPP	Erythrocyte zinc protoporphyrin

MEASUREMENT ABBREVIATIONS

dl	deciliter
ft	feet
g	gram
g/gal	gram/gallon
g/ha·mo	gram/hectare·month
km/hr	kilometer/hour
l/min	liter/minute
mg/km	milligram/kilometer
$\mu g/m^3$	microgram/cubic meter
mm	millimeter
µmol	micrometer
ng/cm^2	nanograms/square centimeter
nm	namometer
nM	nanomole
sec	second

1. EXECUTIVE SUMMARY AND CONCLUSIONS

1.1 INTRODUCTION

This criteria document evaluates and assesses scientific information on the health and welfare effects associated with exposure to various concentrations of lead in ambient air.

According to Section 108 of the Clean Air Act of 1970, as amended in June 1974, a criteria document for a specific pollutant or class of pollutants shall:

> . . . accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities.

Air quality criteria are of necessity based on presently available scientific data, which in turn reflect the sophistication of the technology used in obtaining those data as well as the magnitude of the experimental efforts expended. Thus air quality criteria for atmospheric pollutants are a scientific expression of current knowledge and uncertainties. Specifically air quality criteria are expressions of the scientific knowledge of the relationships between various concentrations--averaged over a suitable time period--of pollutants in the same atmosphere and their adverse effects upon public health and the environment. Criteria are issued as a basis for making decisions about the need for control of a pollutant and as a basis for development of air quality standards governing the pollutant. Air quality criteria are descriptive; that is, they describe the effects that have been observed to occur as a result of external exposure at specific levels of a pollutant. In contrast, air quality standards are prescriptive; that is, they prescribe what a political jurisdiction has determined to be the maximum permissible exposure for a given time in a specified geographic area.

This criteria document is a revision of the previous Air Quality Criteria Document for Lead (EPA-600/8-77-017) published in December, 1977. This revision is mandated by the Clean Air Act (Sect. 108 and 109), as amended U.S.C. §§7408 and 7409. The criteria document sets forth what is known about the effects of lead contamination in the environment on human health and welfare. This requires that the relationship between levels of exposure to lead, via all routes and averaged over a suitable time period, and the biological responses to those levels be carefully assessed. Assessment of exposure must take into consideration the temporal and spatial distribution of lead and its various forms in the environment. Thus, the literature through June, 1983, has been reviewed thoroughly for information relevant to air quality criteria, for lead, but the document is not intended as a complete and detailed review of all literature pertaining to lead. Also, efforts are made to identify major discrepancies in our current knowledge and understanding of the effects of lead compounds.

Lead is a naturally occurring element that may be found in the earth's crust and in all components of the biosphere. It may be found in water, soil, plants, animals, and humans. Because lead also occurs in ore bodies that have been mined for centuries by man, this metal has also been distributed throughout the biosphere by the industrial activities of man. Of particular importance to the human environment are emissions of lead to the atmosphere. The sources of these emissions and the pathways of lead through the environment to man are shown in Figure 1-1. This figure shows natural inputs to soil by crustal weathering and anthropogenic inputs to the atmosphere from automobile emissions and stationary industrial sources. Natural emissions of lead to the atmosphere from volcanoes and windblown soil are of minor importance.

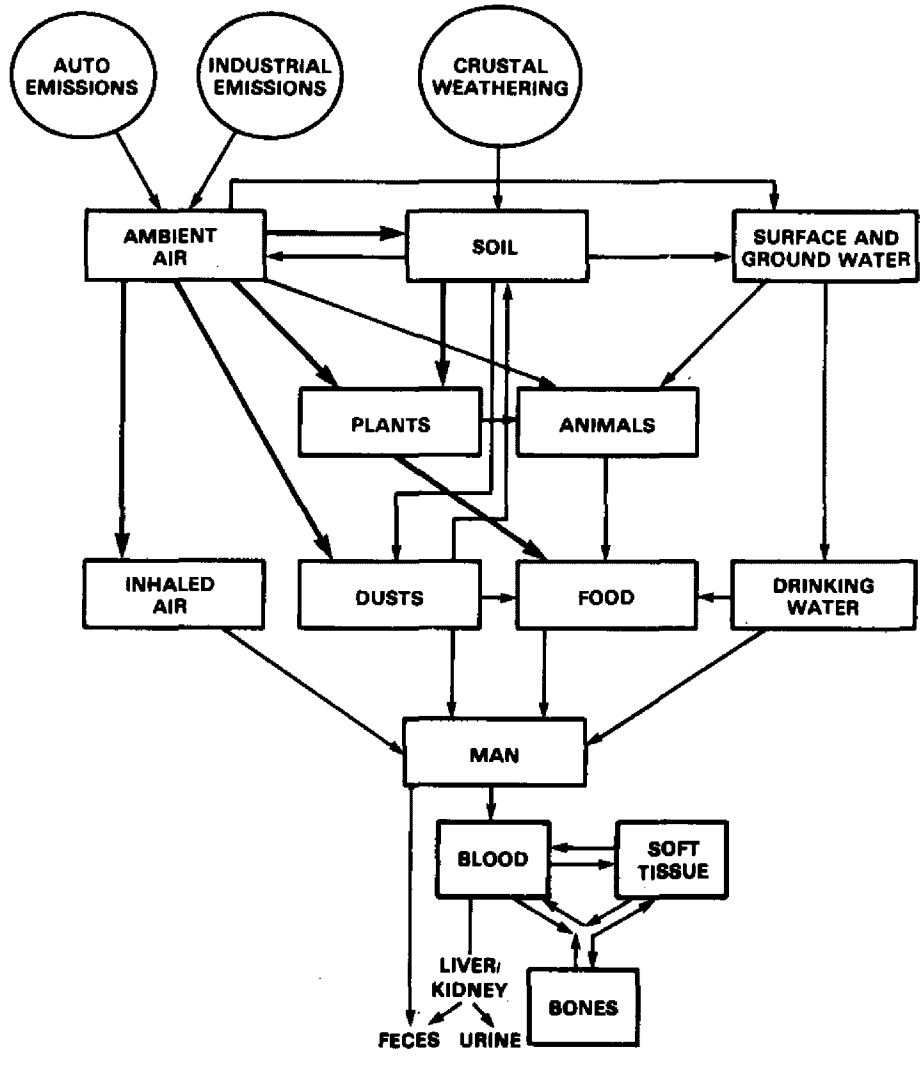

Figure 1-1. Pathways of lead exposure from the environment to man.

From these emission sources, lead moves through the atmosphere to various components of the human environment. Lead is deposited on soil and plants and in animals, becoming incorporated into the food chain of man. Atmospheric lead is a major component of household and street dust; lead is also inhaled directly from the atmosphere.

1.2 ORGANIZATION OF DOCUMENT

This document focuses primarily on lead as found in its various forms in the ambient atmosphere; in order to assess its effects on human health, however, the distribution and biological availability of lead in other environmental media have been considered. The rationale for structuring the document was based primarily on the two major questions of exposure and response. The first portion of the document is devoted to lead in the environment--its physical and chemical properties; the monitoring of lead in various media; sources, emissions, and concentrations of lead; and the transport and transformation of lead within environmental media. The latter portion is devoted to biological responses and effects on human health and ecosystems.

In order to facilitate printing, distribution, and review of the present draft materials, this First External Review Draft of the revised EPA Air Quality Criteria Document for Lead is being released in four volumes. The first volume (Volume I) contains this executive summary and conclusions chapter (Chapter 1) for the entire document. Volume II contains Chapters 2-8, which include: the introduction for the document (Chapter 2); discussions of the above listed topics concerning lead in the environment (Chapters 3-7); and evaluation of lead effects on ecosystems (Chapter 8). The remaining two volumes contain Chapters 9-13, which deal with the extensive available literature relevant to assessment of health effects associated with lead exposure.

An effort has been made to limit the document to a highly critical assessment of the scientific data base. The scientific literature has been reviewed through June 1983. The references cited do not constitute an exhaustive bibliography of all available lead-related literature but they are thought to be sufficient to reflect the current state of knowledge on those issues most relevant to the review of the air quality standard for lead.

The status of control technology for lead is not discussed in this document. For information on the subject, the reader is referred to appropriate control technology documentation published by the Office of Air Quality Planning and Standards (OAQPS), EPA. The subject of "adequate margin of safety" stipulated in Section 108 of the Clean Air Act also is not explicitly addressed here; this topic will be considered in depth by EPA's Office of Air Quality Planning and Standards in documentation prepared as a part of the process of revising the National Ambient Air Quality Standard (NAAQS) for Lead.

1.3 CHEMICAL AND PHYSICAL PROPERTIES OF LEAD

Lead is a gray-white metal of bright luster that, because of its easy isolation and low melting point, was among the first of the metals to be extensively utilized by man. Lead was used as early as 2000 B.C. by the Phoenicians. The most abundant ore is galena, from which metallic lead is readily smelted. The metal is soft, malleable, and ductile, a poor electrical conductor, and highly impervious to corrosion. This unique combination of physical properties has led to its use in piping and roofing, and in containers for corrosive liquids. The metal and the dioxide are used in storage batteries, and organolead compounds are used in gasoline additives to boost octane levels. Since lead occurs in highly concentrated ores from which it is readily separated, the availability of lead is far greater than its natural abundance would suggest. The great environmental significance of lead is the result both of its utility and of its availability.

The properties of organolead compounds (i.e., compounds containing bonds between lead and carbon) are entirely different from those of the inorganic compounds of lead. Because of their use as antiknock agents in gasoline and other fuels, the most important organolead compounds have been the tetraalkyl compounds tetraethyllead (TEL) and tetramethyllead (TML). These lead compounds are removed from internal combustion engines by a process called lead scavenging, in which they react in the combustion chamber with halogenated hydrocarbon additives (notably ethylene dibromide and ethylene dichloride) to form lead halides, usually bromochlorolead(II).

The donor atoms in a metal complex could be almost any basic atom or molecule; the only requirement is that a donor, usually called a ligand, must have a pair of electrons available for bond formation. In general, the metal atom occupies a central position in the complex, as exemplified by the lead atom in tetramethyllead (Figure 1-2a) which is tetrahedrally surrounded by four methyl groups. In these simple organolead compounds, the lead is usually present as Pb(IV), and the complexes are relatively inert. These simple ligands, which bind to metal at only a single site, are called monodentate ligands. Some ligands, however, can bind to the metal atom by more than one donor atom, so as to form a heterocyclic ring structure. Rings of this general type are called chelate rings, and the donor molecules which form them are called polydentate ligands or chelating agents. In the chemistry of lead, chelation normally involves Pb(II). A wide variety of biologically significant chelates with ligands such as amino acids, peptides, and nucleotides are known. The simplest structure of this type occurs with the amino acid glycine, as represented in Figure 1-2b for a 1:2 (metal:ligand) complex. The importance of chelating agents in the present context is their widespread use in the treatment of lead and other metal poisoning.

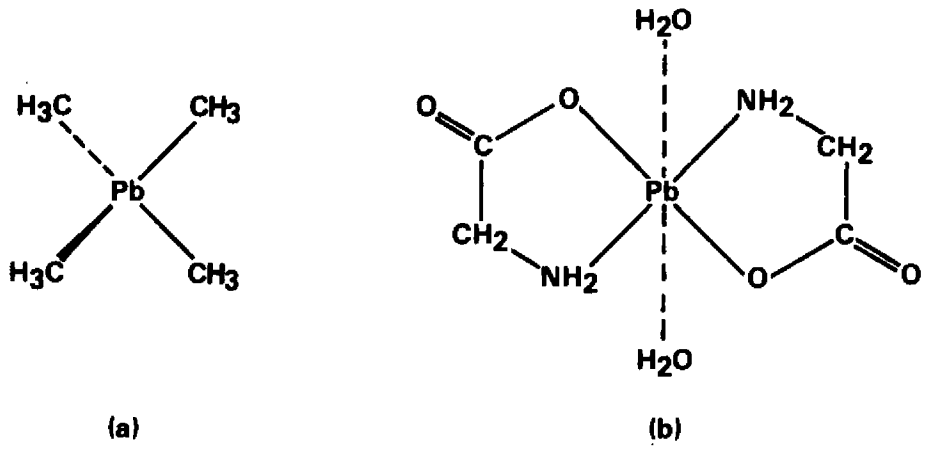

Figure 1-2. Metal complexes of lead.

Metals are often classified according to some combination of their electronegativity, ionic radius, and formal charge. These parameters are used to construct empirical classification schemes of relative hardness or softness. In these schemes, "hard" metals form strong bonds with "hard" anions and, likewise, "soft" metals bond with "soft" anions. Some metals are borderline, having both soft and hard character. Pb(II), although borderline, demonstrates primarily soft character (Figure 1-3). The term Class A may also be used to refer to hard metals, and Class B to soft metals. Since Pb(II) is a relatively soft (or class B) metal ion, it forms strong bonds to soft donor atoms like the sulfur atoms in the cysteine residues of proteins and enzymes. In living systems, lead atoms bind to these peptide residues in proteins, thereby changing the tertiary structure of the protein or blocking a substrate's approach to the active site of an enzyme. This prevents the proteins from carrying out their functions. As has been demonstrated in several studies (Jones and Vaughn, 1978; Williams and Turner, 1981; Williams et al., 1982), there is an inverse correlation between the LD_{50} values of metal complexes and the chemical softness parameter. Lead(II) has a higher softness parameter than either cadmium(II) or mercury(II), so lead(II) compounds would not be expected to be as toxic as their cadmium or mercury analogues.

The role of the chelating agents is to compete with the peptides for the metal by forming stable chelate complexes that can be transported from the protein and eventually be excreted by the body. For simple thermodynamic reasons, chelate complexes are much more stable than monodentate metal complexes, and it is this enhanced stability that is the basis for their ability to compete favorably with proteins and other ligands for the metal ions.

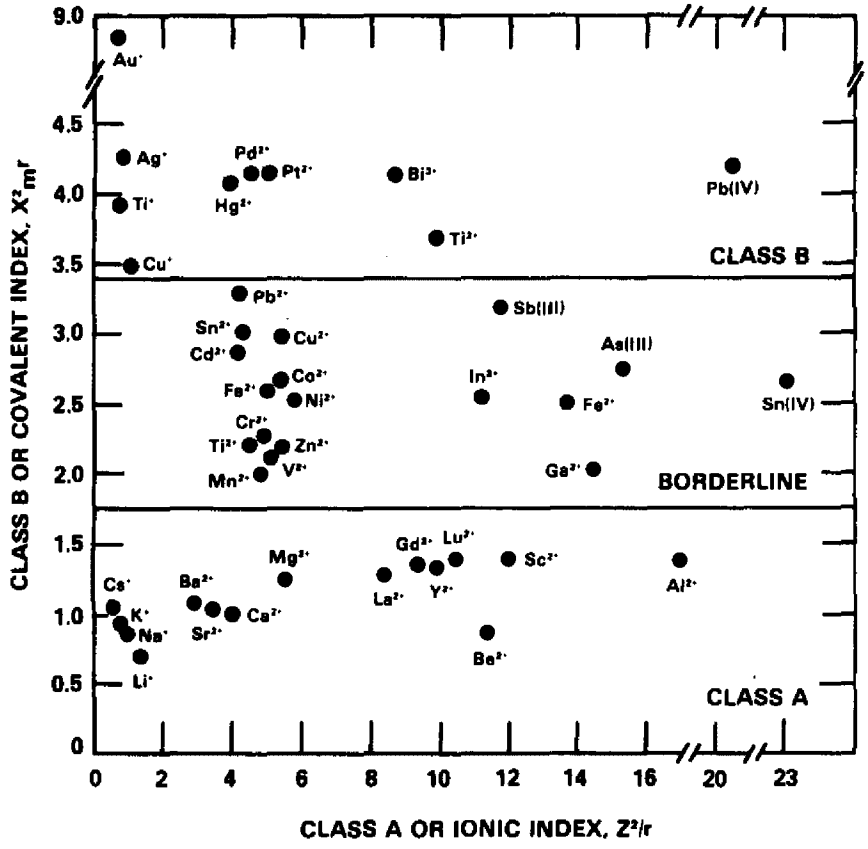

Figure 1-3. Softness parameters of metals.

Source: Nieboer and Richardson (1980).

It should be noted that both the stoichiometry and structures of metal chelates depend upon pH, and that structures different from those manifest in solution may occur in crystals. It will suffice to state, however, that several ligands can be found that are capable of sufficiently strong chelation with lead present in the body under physiological conditions to permit their use in the effective treatment of lead poisoning.

1.4 SAMPLING AND ANALYTICAL METHODS FOR ENVIRONMENTAL LEAD

Lead, like all criteria pollutants, has a designated Reference Method for monitoring and analysis as required in State Implementation Plans for determining compliance with the lead National Ambient Air Quality Standard. The Reference Method uses a high volume sampler (hi-vol) for sample collection and atomic absorption spectrometry (AAS) for analysis.

For a rigorous quality assurance program, it is essential that investigators recognize all sources of contamination and use every precaution to eliminate them. Contamination occurs

on the surfaces of collection containers and devices, on the hands and clothing of the investigator, in the chemical reagents, in the laboratory atmosphere, and on the labware and tools used to prepare the sample for analysis.

1.4.1 Sampling Techniques

Sampling strategy encompasses site selection, choice of instrument used to obtain representative samples, and choice of method used to preserve sample integrity. In the United States, some sampling stations for air pollutants have been operated since the early 1950's. These early stations were a part of the National Air Surveillance Network (NASN), which has now become the National Filter Analysis Network (NFAN). Two other types of networks have been established to meet specific data requirements. State and Local Air Monitoring Stations (SLAMS) provide data from specific areas where pollutant concentrations and population densities are the greatest and where monitoring of compliance to standards is critical. The National Air Monitoring Station (NAMS) network is designed to serve national monitoring needs, including assessment of national ambient trends. SLAMS and NAMS stations are maintained by state and local agencies and the air samples are analyzed in their laboratories. Stations in the NFAN network are maintained by state and local agencies, but the samples are analyzed by laboratories in the U.S. Environmental Protection Agency, where quality control procedures are rigorously maintained.

Data from all three networks are combined into one data base, the National Aerometric Data Bank (NADB). These data may be individual chemical analyses of a 24-hour sampling period arithmetically averaged over a calendar period, or chemical composites of several filters used to determine a quarterly composite. Data are occasionally not available for a given location because they do not conform to strict statistical requirements.

In September, 1981, EPA promulgated regulations establishing ambient air monitoring and data reporting requirements for lead comparable to those already established in May of 1979 for the other criteria pollutants. Whereas sampling for lead is accomplished when sampling for total suspended particulate (TSP), the designs of lead and TSP monitoring stations must be complimentary to insure compliance with the NAMS criteria for each pollutant.

There must be at least two SLAMS sites for lead in any area that has a population greater than 500,000 and any area where lead concentration currently exceeds the ambient lead standard (1.5 $\mu g/m^3$) or has exceeded it since January 1, 1974.

To clarify the relationship between monitoring objectives and the actual siting of a monitor, the concept of a spatial scale of representativeness was developed. The spatial scales are discribed in terms of the physical dimensions of the air space surrounding the monitor throughout which pollutant concentrations are fairly similar.

The time scale may also be an important factor. Siting criteria must include sampling times sufficiently long to include average windspeed and direction, or a sufficient number of samples must be collected over short sampling periods to provide an average value consistent with a 24-hour exposure.

Airborne lead is primarily inorganic particulate matter but may occur in the form of organic gases. Devices used for collecting samples of ambient atmospheric lead include the standard hi-vol sampler and a variety of other collectors employing filters, impactors, impingegers, or scrubbers, either separately or in combination, that measure lead in $\mu g/m^3$. Some samplers measure lead deposition expressed in $\mu g/cm^2$; some instruments separate particles by size. As a general rule, particles smaller in aerodynamic diameter than 2.5 μm are classified as "fine", and those larger than 2.5 μm as "coarse."

The present SLAMS and NAMS employ the standard hi-vol sampler (U.S. Environmental Protection Agency, 1971) as part of their sampling networks. As a Federal Reference Method Sampler, the hi-vol operates with a specific flow rate of 1600 to 2500 m^3 of air per day

When sampling ambient lead with systems employing filters, it is likely that vapor-phase organolead compounds will pass through the filter media. The use of bubblers downstream from the filter containing a suitable reagent or absorber for collection of these compounds has been shown to be effective. Organolead may be collected on iodine crystals, adsorbed on activated charcoal, or absorbed in an iodine monochloride solution. In one experiment, Purdue et al. (1973) operated two bubblers in series containing iodine monochloride solution. One hundred percent of the lead was recovered in the first bubbler.

Sampling of stationary sources for lead requires the use of a sequence of samplers in the smokestack. Since lead in stack emissions may be present in a variety of physical and chemical forms, source sampling trains must be designed to trap and retain both gaseous and particulate lead.

Three principal procedures have been used to obtain samples of auto exhaust aerosols for subsequent analysis for lead compounds: a horizontal dilution tunnel, plastic sample collection bags, and a low residence time proportional sampler. In each procedure, samples are air diluted to simulate roadside exposure conditions. In the most commonly used procedure, the air dilution tube segregates fine combustion-derived particles from larger lead particles. Such tunnels of varying lengths have been limited by exhaust temperatures to total flows above approximately 11 m^3/min. Similar tunnels have a centrifugal fan located upstream, rather than a positive displacement pump located downstream. This geometry produces a slight positive pressure in the tunnel and expedites transfer of the aerosol to holding chambers for studies of aerosol growth. However, turbulence from the fan may affect the sampling efficiency. Since the total exhaust plus dilution airflow is not held constant in this system, potential errors can be reduced by maintaining a very high dilution air/exhaust flow ratio.

In the bag technique, auto emissions produced during simulated driving cycles are air-diluted and collected in a large plastic bag. The aerosol sample is passed through a filtration or impaction sampler prior to lead analysis. This technique may result in errors of aerosol size analysis because of condensation of low vapor pressure organic substances onto the lead particles.

To minimize condensation problems, a third technique, a low residence time proportional sampling system, has been used. It is based on proportional sampling of raw exhaust, again diluted with ambient air followed by filtration or impaction. Since the sample flow must be a constant proportion of the total exhaust flow, this technique may be limited by the response time of the equipment to operating cycle phases that cause relatively small transients in the exhaust flow rate.

Other primary environmental media that may be affected by airborne lead include precipitation, surface water, soil, vegetation, and foodstuffs. The sampling plans and the sampling methodologies used in dealing with these media depend on the purpose of the experiments, the types of measurements to be carried out, and the analytical technique to be used.

Lead at the start of a rain event is higher in concentration than at the end, and rain striking the canopy of a forest may rinse dry deposition particles from the leaf surfaces. Rain collection systems should be designed to collect precipitation on an event basis and to collect sequential samples during the event.

Two automated systems have recently been used. The Sangamo Precipitation Collector, Type A, collects rain in a single bucket exposed at the beginning of the rain event (Samant and Vaidya, 1982). A second sampler, described by Coscio et al. (1982), also remains covered between rain events; it can collect a sequence of eight samples during the period of rain and may be fitted with a refrigeration unit for sample cooling.

Because the physicochemical form of lead often influences environmental effects, there is a need to differentiate among the various chemical forms. Complete differentiation among all such forms is a complex task that has not yet been fully accomplished. The most commonly used approach is to distinguish between dissolved and suspended forms of lead. All lead passing through a 0.45 μm membrane filter is operationally defined as dissolved, while that retained on the filter is defined as suspended (Kopp and McKee, 1979).

Containers used for sample collection and storage should be fabricated from essentially lead-free plastic or glass, e.g., conventional polyethylene, Teflon®, or quartz. These containers must be leached with hot acid for several days to ensure minimum lead contamination (Patterson and Settle, 1976).

The distance from emission sources and depth gradients associated with lead in soil must be considered in designing the sampling plan. Vegetation, litter, and large objects such as

stones should not be included in the sample. Depth samples should be collected at not greater than 2 cm intervals to preserve vertical integrity.

Because most soil lead is in chemical forms unavailable to plants, and because lead is not easily transported by plants, roots typically contain very little lead and shoots even less. Before analysis, a decision must be made as to whether or not the plant leaf material should be washed to remove surface contamination from dry deposition and soil particles. If the plants are sampled for total lead content (e.g., if they serve as animal food sources), they cannot be washed; if the effect of lead on internal plant processes is being studied, the plant samples should be washed. In either case, the decision must be made at the time of sampling, as washing cannot be effective after the plant materials have dried.

In sampling for airborne lead, air is drawn through filter materials such as glass fiber, cellulose acetate, or porous plastic. These materials often include contaminant lead that can interfere with the subsequent analysis. Procedures for cleaning filters to reduce the lead blank rely on washing with acids or complexing agents. The type of filter and the analytical method to be used often determines the ashing technique. In some methods, e.g., X-ray fluorescence, analysis can be performed directly on the filter if the filter material is suitable. Skogerboe (1974) provided a general review of filter materials.

The main advantages of glass fiber filters are low pressure drop and high particle collection efficiency at high flow rates. The main disadvantage is variability in the lead blank, which makes their use inadvisable in many cases. This has placed a high priority on the standardization of a suitable filter for hi-vol samples. Other investigations have indicated, however, that glass fiber filters are now available that do not present a lead interference problem (Scott et al., 1976b). Teflon® filters have been used since 1975 by Dzubay et al. (1982) and Stevens et al. (1978), who have shown these filters to have very low lead blanks (<2 ng/cm^2). The collection efficiencies of filters, and also of impactors, have been shown to be dominant factors in the quality of the derived data.

1.4.2 Analytical Procedures

The choice of analytical method depends on the nature of the data required, the type of sample being analyzed, the skill of the analyst, and the equipment available. For general determination of elemental lead, atomic absorption spectroscopy (AAS) is widely used and recommended (C.F.R., 1982 40: § 50). Optical emission spectrometry and X-ray fluorescence (XRF) are rapid and inexpensive methods for multielemental analyses. X-ray fluorescence can measure lead concentrations reliably to 1 ng/m^3 using samples collected with commercial dichotomous samplers. Other analytical methods have specific advantages appropriate for special studies.

With respect to measuring lead without contamination during sampling or from the laboratory, several investigators have shown that the magnitude of the problem is quite large. It appears that the problem may be caused by failure to control the blank or by failure to standardize instrument operation (Patterson, 1983; Skogerboe, 1982). The laboratory atmosphere, collecting containers, and the labware used may be primary contributors to the lead blank problem (Patterson, 1983; Skogerboe, 1982). Failure to recognize these and other sources of contamination such as reagents and hand contact is very likely to result in the generation of artificially high analytical results. Samples with less than 100 ng lead should be analyzed in a clean laboratory especially designed for the elimination of lead contamination. Moody (1982) has described the construction and application of such a laboratory at the National Bureau of Standards.

For AAS, the lead atoms in the sample must be vaporized either in a precisely controlled flame or in a furnace. Furnace systems in AAS offer high sensitivity as well as the ability to analyze small samples. These enhanced capabilities are offset in part by greater difficulty in analytical calibration and by loss of analytical precision.

Particles may also be collected on cellulose acetate filters. Disks (0.5 cm^2) are punched from these filters and analyzed by insertion of nichrome cups containing the disks into a flame. Another application involves the use of graphite cups as particle filters with the subsequent analysis of the cups directly in the furnace system. These two procedures offer the ability to determine particulate lead directly with minimal sample handling.

In an analysis using AAS and hi-vol samplers, atmospheric concentrations of lead were found to be 0.076 ng/m^3 at the South Pole (Maenhaut et al., 1979). Lead analyses of 995 particulate samples from the NASN were accomplished by AAS with an indicated precision of 11 percent (Scott et al., 1976a). More specialized AAS methods for the determination of tetraalkyl lead compounds in water and fish tissue have been described by Chau et al. (1979) and in air by Birnie and Noden (1980) and Rohbock et al. (1980).

Techniques for AAS are still evolving. An alternative to the graphite furnace, evaluated by Jin and Taga (1982), uses a heated quartz tube through which the metal ion in gaseous hydride form flows continuously. Sensitivities were 1 to 3 ng/g for lead. The technique is similar to the hydride generators used for mercury, arsenic, and selenium. Other nonflame atomization systems, electrodeless discharge lamps, and other equipment refinements and technique developments have been reported (Horlick, 1982).

Optical emission spectroscopy is based on the measurement of the light emitted by elements when they are excited in an appropriate energy medium. The technique has been used to determine the lead content of soils, rocks, and minerals at the 5 to 10 µg/g level with a relative standard deviation of 5 to 10 percent; this method has also been applied to the analysis of a large number of air samples (Sugimae and Skogerboe, 1978). The primary advantage

of this method is that it allows simultaneous measurement of a large number of elements in a small sample. In a study of environmental contamination by automotive lead, sampling times were shortened by using a sampling technique in which lead-free porous graphite was used both as the filter medium and as the electrode in the spectrometer. Lead concentrations of 1 to 10 $\mu g/m^3$ were detected after a half-hour flow at 800 to 1200 ml/min through the filter.

More recent activities have focused attention on the inductively coupled plasma (ICP) system as a valuable means of excitation and analysis (Garbarino and Taylor, 1979). The ICP system offers a higher degree of sensitivity with less analytical interference than is typical of many of the other emission spectroscopic systems. Optical emission methods are inefficient when used for analysis of a single element, since the equipment is expensive and a high level of operator training is required. This problem is largely offset when analysis for several elements is required, as is often the case for atmospheric aerosols. X-ray fluorescence (XF) allows simultaneous identification of several elements, including lead, using a high-energy irradiation source. With the X-ray tubes coupled with fluorescers, very little energy is transmitted to the sample; thus sample degradation is kept to a minimum. Electron beams and radioactive isotope sources have been used extensively as energy sources for XRF analysis.

X-ray emission induced by charged-particle excitation (proton-induced X-ray emission or PIXE) offers an attractive alternative to the more common techniques. The excellent capability of accelerator beams for X-ray emission analysis is partially due to the relatively low background radiation associated with the excitation.

X-radiation is the basis of the electron microprobe method of analysis. When an intense electron beam is incident on a sample, it produces several forms of radiation, including X-rays, whose wavelengths depend on the elements present in the material and whose intensities depend on the relative quantities of these elements. The method is unique in providing compositional information on individual lead particles, thus permitting the study of dynamic chemical changes and perhaps allowing improved source identification.

Isotope dilution mass spectrometry (IDMS) is the most accurate measurement technique known at the present time. No other techniques serve more reliably as a comparative reference; it has been used for analyses of subnanogram concentrations of lead in a variety of sample types (Chow et al., 1969, 1974; Facchetti and Geiss, 1982; Hirao and Patterson, 1974; Murozumi et al., 1969; Patterson et al., 1976; Rabinowitz et al., 1973). The isotopic composition of lead peculiar to various ore bodies and crustal sources may also be used as a means of tracing the origin of anthropogenic lead.

Colorimetric or spectrophotometric analysis for lead using dithizone (diphenylthiocarbazone) as the reagent has been used for many years. It was the primary method recommended by a National Academy of Sciences (1972) report on lead, and the basis for the tentative method of

testing for lead in the atmosphere by the American Society for Testing Materials (1975b). Prior to the development of the IDMS method, colorimetric analysis served as the reference by which other methods were tested.

Analytical methods based on electrochemical phenomena are found in a variety of forms. They are characterized by a high degree of sensitivity, selectivity, and accuracy derived from the relationship between current, charge, potential, and time for electrolytic reactions in solutions. Anodic stripping voltammetry (ASV) is a two step process in which the lead is preconcentrated onto a mercury electrode by an extended but selected period of reduction. After the reduction step, the potential is scanned either linearly or by differential pulse to oxidize the lead and allow measurement of the oxidation (stripping) current.

The majority of analytical methods are restricted to measurement of total lead and cannot directly identify the various compounds of lead. Gas chromatography (GC) using the electron capture detector has been demonstrated to be useful for organolead compounds. The use of atomic absorption as the GC detector for organolead compounds has been described by De Jonghe et al. (1981), while a plasma emission detector has been used by Estes et al. (1981). In addition, Messman and Rains (1981) have used liquid chromatography with an atomic absorption detector to measure organolead compounds. Mass spectrometry may also be used with gas chromatography (Mykytiuk et al., 1980).

1.5 SOURCES AND EMISSIONS

The history of global lead emissions has been assembled from chronological records of deposition in polar snow strata, marine and freshwater sediments, and the annual rings of trees. These records aid in establishing natural background levels of lead in air, soils, plants, animals, and humans, and they document the sudden increase in atmospheric lead at the time of the industrial revolution, with a later burst during the 1920's when lead-alkyls were first added to gasoline. Pond sediment analyses have shown a 20-fold increase in lead deposition during the last 150 years (Figure 1-4), documenting not only the increasing use of lead since the beginning of the industrial revolution in western United States, but also the relative fraction of natural vs. anthropogenic lead inputs. Other studies have shown the same magnitude of increasing deposition in freshwater marine sediments. The pond and marine sediments also document the shift in isotopic composition of atmospheric caused by increased commercial use of the New Lead Belt in Missouri, where the ore body has an isotopic composition substantially different from other ore bodies of the world.

Perhaps the best chronological record is that of the polar ice strata of Murozumi et al. (1969), which extends nearly three thousand years back in time (Figure 1-4). At the South

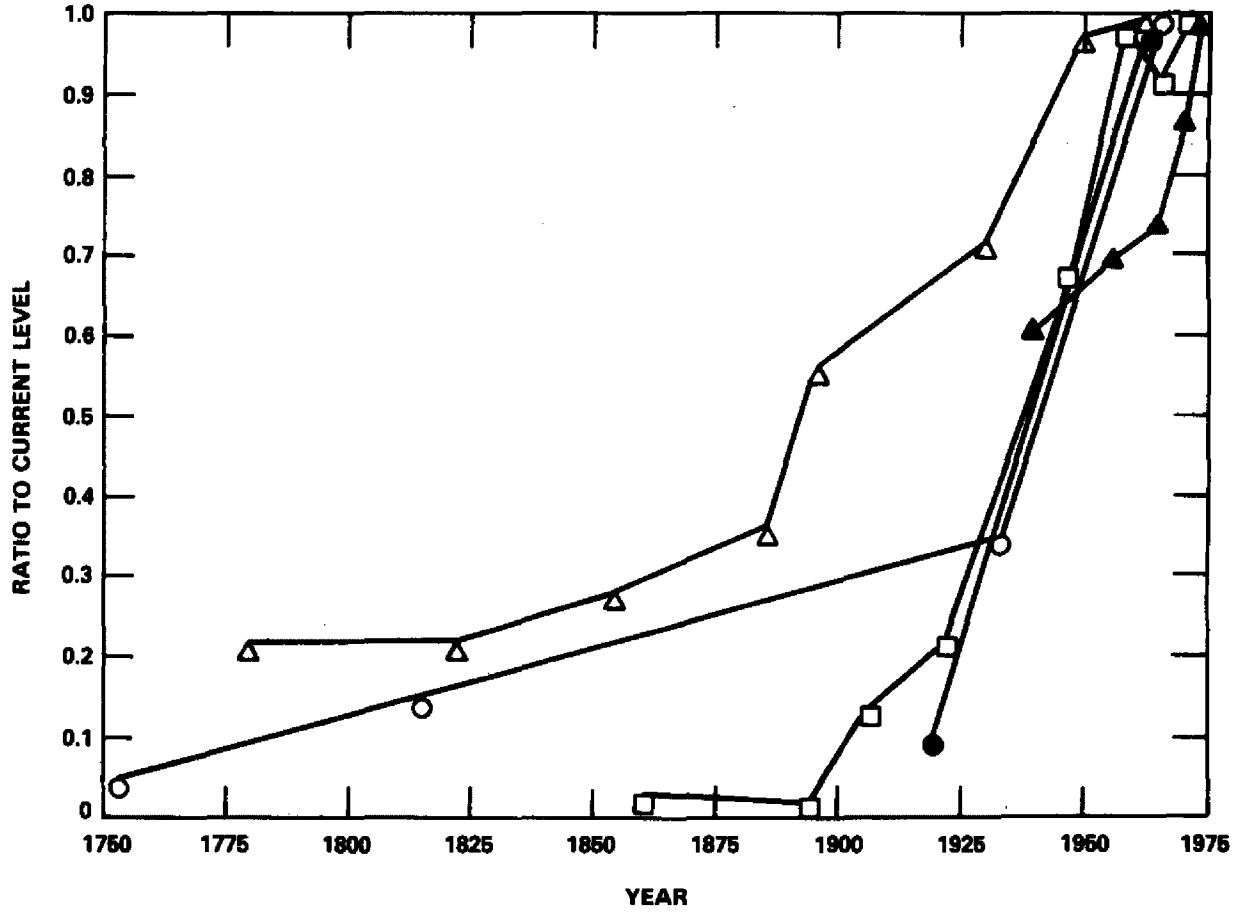

Figure 1-4. Chronological record of the relative increase of lead in snow strata, pond and lake sediments, marine sediments, and tree rings. The data are expressed as a ratio of the latest year of the record and should not be interpreted to extend back in time to natural or uncontaminated levels of lead concentration.

Source: Adapted from Murozumi et al. (1969) (○), Shirahata et al. (1980) (□), Edgington and Robbins (1976) (△), Ng and Patterson (1982) (▲), and Rolfe (1974) (●).

Pole, Boutron (1982) observed a 4-fold increase of lead in snow from 1957 to 1977 but saw no increase during the period 1927 to 1957. The author suggested the extensive atmospheric lead pollution which began in the 1920's did not reach the South Pole until the mid-1950's. This interpretation agrees with that of Maenhaut et al. (1979), who found atmospheric concentrations of lead of 0.000076 $\mu g/m^3$ at the same location. This concentration is about 3-fold higher than the 0.000024 $\mu g/m^3$ estimated by Patterson (1980) and Servant (1982) to be the natural lead concentration in the atmosphere. In summary, it is likely that atmospheric lead emissions have increased 2000-fold since the pre-Roman era, that even at this early time the atmosphere may have been contaminated by a factor of three over natural levels (Murozumi et al. 1969), and that global atmospheric concentrations have increased dramatically since the 1920's.

The history of global emissions may also be inferred from total production of lead. The historical picture of lead production has been pieced together from many sources by Settle and Patterson (1980) (Figure 1-5). Until the industrial revolution, lead production was determined largely by the ability or desire to mine lead for its silver content. Since that time, lead has been used as an industrial product in its own right, and efforts to improve smelter efficiency, including control of stack emissions and fugitive dusts, have made lead production more economical. This improved efficiency is not reflected in the chronological record because of atmospheric emissions of lead from many other anthropogenic sources, especially gasoline combustion (see Section 5.3.3). From this knowledge of the chronological record, it is possible to sort out contemporary anthropogenic emissions from natural sources of atmospheric lead.

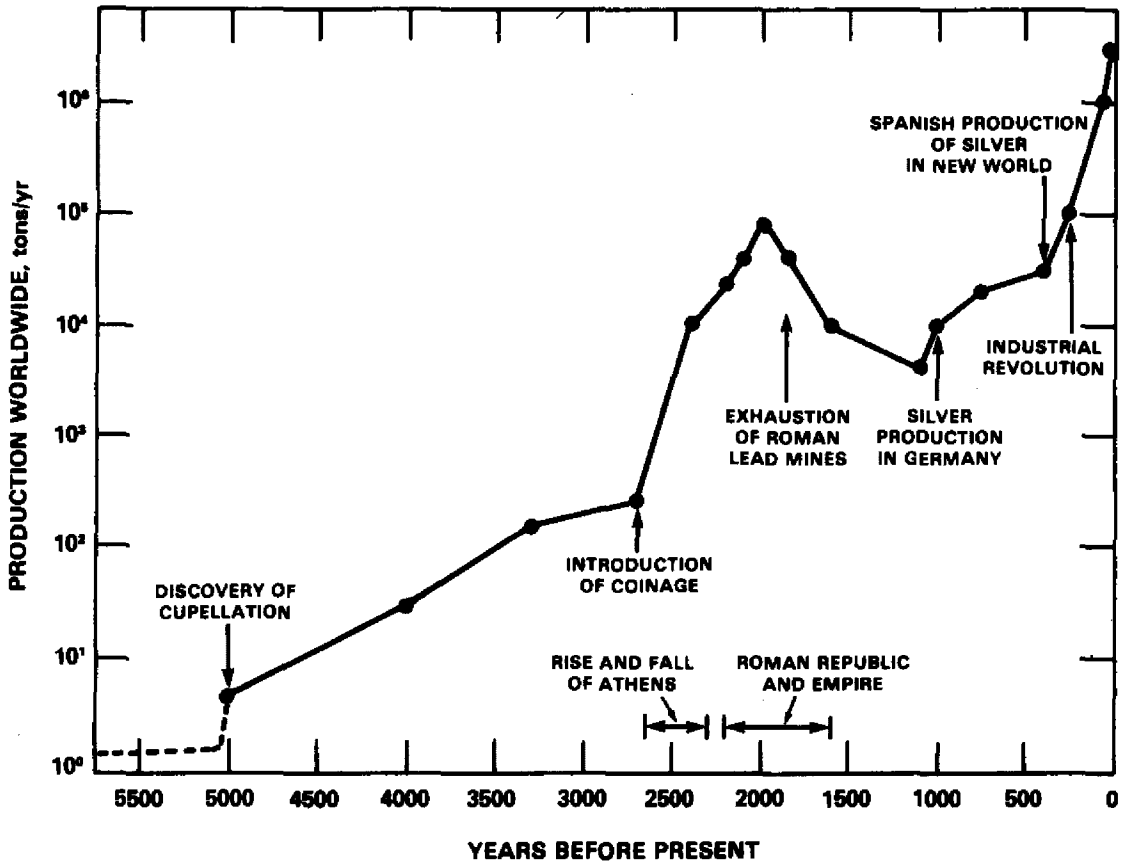

Figure 1-5. The global lead production has changed historically in response to major economic and political events. Increases in lead production (note log scale) correspond approximately to historical increases in lead emissions shown in Figure 5-1.

Source: Adapted from Settle and Patterson (1980).

Lead enters the biosphere from lead-bearing minerals in the lithosphere through both natural and man-made processes. Measurements of soil materials taken at 20-cm depths in the continental United States show a median lead concentration of 15 to 16 μg Pb/g soil. In natural processes, lead is first incorporated in soil in the active root zone, from which it may be absorbed by plants, leached into surface waters, or eroded into windborne dusts.

Calculations of natural contributions using geochemical information indicate that natural sources contribute a relatively small amount of lead to the atmosphere. It has been estimated from geochemical evidence that the natural particulate lead level is less than 0.0005 $\mu g/m^3$ (National Academy of Sciences, 1980), and probably lower than the 0.000076 $\mu g/m^3$ measured at the South Pole (Maenhaut et al., 1979). In contrast, average lead concentrations in urban suspended particulate matter range as high as 6 $\mu g/m^3$ (U.S. Environmental Protection Agency, 1979, 1978). Evidently, most of this urban particulate lead originates from man-made sources.

Lead occupies an important position in the U.S. economy, ranking fifth among all metals in tonnage used. Approximately 85 percent of the primary lead produced in this country is from native mines, although often associated with minor amounts of zinc, cadmium, copper, bismuth, gold, silver, and other minerals (U.S. Bureau of Mines, 1972-1982). Missouri lead ore deposits account for approximately 80 to 90 percent of the domestic production. Total utilization averaged approximately 1.36×10^6 t/yr over the 10-year period, with storage batteries and gasoline additives accounting for ~70 percent of total use. Certain products, especially batteries, cables, plumbing, weights, and ballast, contain lead that is economically recoverable as secondary lead. Lead in pigments, gasoline additives, ammunition, foil, solder, and steel products is widely dispersed and therefore is largely unrecoverable. Approximately 40-50 percent of annual lead production is recovered and eventually recycled.

Lead or its compounds may enter the environment at any point during mining, smelting, processing, use, recycling, or disposal. Estimates of the dispersal of lead emissions into the environment by principal sources indicate that the atmosphere is the major initial recipient. Estimated lead emissions to the atmosphere are shown in Table 1-1. Mobile and stationary sources of lead emissions, although found throughout the nation, tend to be concentrated in areas of high population density, and near smelters. Figure 1-6 shows the approximate locations of major lead mines, primary and secondary smelters and refineries, and alkyl lead paints (International Lead Zinc Research Organization, 1982).

The majority of lead compounds found in the atmosphere result from leaded gasoline combustion. Several reports indicate that transportation sources contribute over 80 percent of the total atmospheric lead. Other mobile sources, including aviation use of leaded gasoline and diesel and jet fuel combustion, contribute insignificant lead emissions to the atmosphere.

Automotive lead emissions occur as PbBrCl in fresh exhaust particles. The fate of emitted lead particles depends upon particle size. Particles initially formed by condensation of

TABLE 1-1. ESTIMATED ATMOSPHERIC LEAD EMISSIONS FOR THE UNITED STATES, 1981 AND THE WORLD

Source Category	Annual U.S. Emissions (t/yr)	Percentage of U.S. Total Emissions	Annual Global Emissions (t/yr)
Gasoline combustion	35,000	85.9	273,000
Waste oil combustion	830	2.0	8,900
Solid waste disposal	319	0.8	
Coal combustion	950	2.3	14,000
Oil combustion	226	0.6	6,000
Wood combustion	--	--	4,500
Gray iron production	295	0.7	50,000
Iron and steel production	533	1.3	
Secondary lead smelting	631	1.5	770
Primary copper smelting	30	0.1	27,000
Ore crushing and grinding	326	0.8	8,200
Primary lead smelting	921	2.3	31,000
Other metallurgical	54	0.1	
Zn smelting			16,000
Ni smelting			2,500
Lead alkyl manufacture	245	0.6	
Type metal	85	0.2	7,400
Portland cement production	71	0.2	
Miscellaneous	233	0.5	5,900
Total	40,739[a]	100%	449,170

[a]Inventory does not include emissions from exhausting workroom air, burning of lead-painted surfaces, welding of lead-painted steel structures, or weathering of painted surfaces.

Source: For U.S. emissions, Battye (1983); for global emissions, Nriagu (1979).

lead compounds in the combustion gases are quite small (well under 0.1 μm in diameter). Particles in this size category are subject to growth by coagulation and, when airborne, can remain suspended in the atmosphere for 7 to 30 days and travel thousands of miles from their original source. Larger particles are formed as the result of agglomeration of smaller condensation particles and have limited atmospheric lifetimes.

During the lifetime of the vehicle, approximately 35 percent of the lead contained in the gasoline burned by the vehicle will be emitted as small particles [<0.25 μm mass median equivalent diameter (MMED)], and approximately 40 percent will be emitted as larger particles

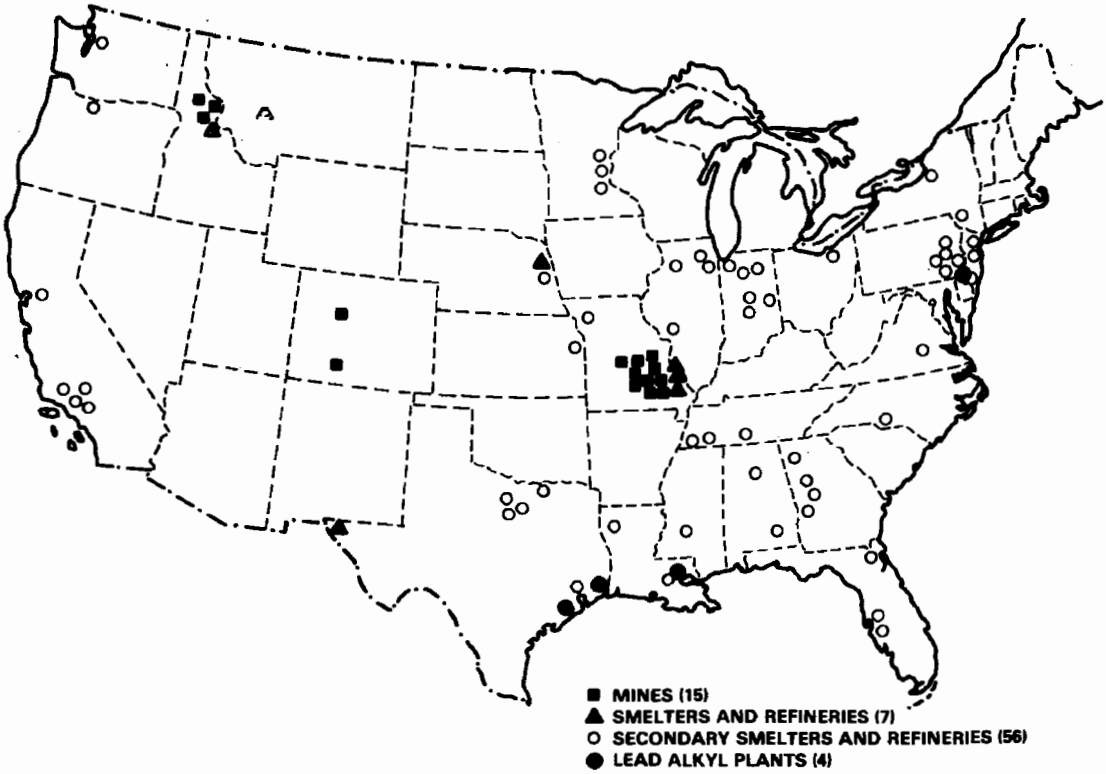

Figure 1-6. Locations of major lead operations in the United States.

Source: International Lead Zinc Research Organization (1982).

(>10 μm MMED) (Ter Haar et al., 1972). The remainder of the lead consumed in gasoline combustion is deposited in the engine and exhaust system.

Although the majority (>90 percent on a mass basis) of vehicular lead compounds are emitted as inorganic particles (e.g., PbBrCl), some organolead vapors (e.g., lead alkyls) are also emitted. The largest volume of organolead vapors arises from the manufacture, transport, and handling of leaded gasoline. Such vapors are photoreactive, and their presence in local atmospheres is transitory. Organolead vapors are most likely to occur in occupational settings and have been found to contribute less than 10 percent of the total lead present in the atmosphere.

The use of lead additives in gasoline, which increased in volume for many years, is now decreasing as automobiles designed to use unleaded fuel constitute the major portion of the automotive population. The decline in the use of leaded fuel is the result of two regulations promulgated by the U.S. Environmental Protection Agency (F.R., 1973 December 6). The first required the availability of unleaded fuel for use in automobiles designed to meet federal emission standards with lead-sensitive emission control devices (e.g., catalytic converters); the second required a reduction or phase-down of the lead content in leaded gasoline. Compliance with the phase-down of lead in gasoline has recently been the subject of proposed rulemakings. The final action (F.R., 1982 October 29) replaced the present 0.5 g/gal standard for the average lead content of all gasoline with a two-tiered standard for the lead content of leaded gasoline. Under this proposed rule, refineries would be required to meet a standard of 1.10 g/gal for leaded gasoline while maintaining an average 0.5 g/gal for all gasoline.

The trend in lead content for U.S. gasolines is shown in Figure 1-7. Of the total gasoline pool, which includes both leaded and unleaded fuels, the average lead content has decreased 63 percent, from an average of 1.62 g/gal in 1975 to 0.60 g/gal in 1981.

Data describing the lead consumed in gasoline and average ambient lead levels (composite of maximum quarterly values) versus calendar year are plotted in Figure 1-8. The linear correlation between lead consumed in gasoline and the composite maximum average quarterly ambient average lead level is very good. Between 1975 and 1980, the lead consumed in gasoline decreased 52 percent (from 165,577 metric tons to 78,679 metric tons) while the corresponding composite maximum quarterly average of ambient lead decreased 51 percent (from 1.23 $\mu g/m^3$ to 0.60 $\mu g/m^3$). This indicates that control of lead in gasoline over the past several years has effected a direct decrease in peak ambient lead concentrations.

Furthermore, the equation in Figure 1-8 implies that the complete elimination of lead from gasoline might reduce the composite average of the maximum quarterly lead concentrations at these stations to 0.05 $\mu g/m^3$, a level typical of concentrations reported for nonurban stations in the U.S.

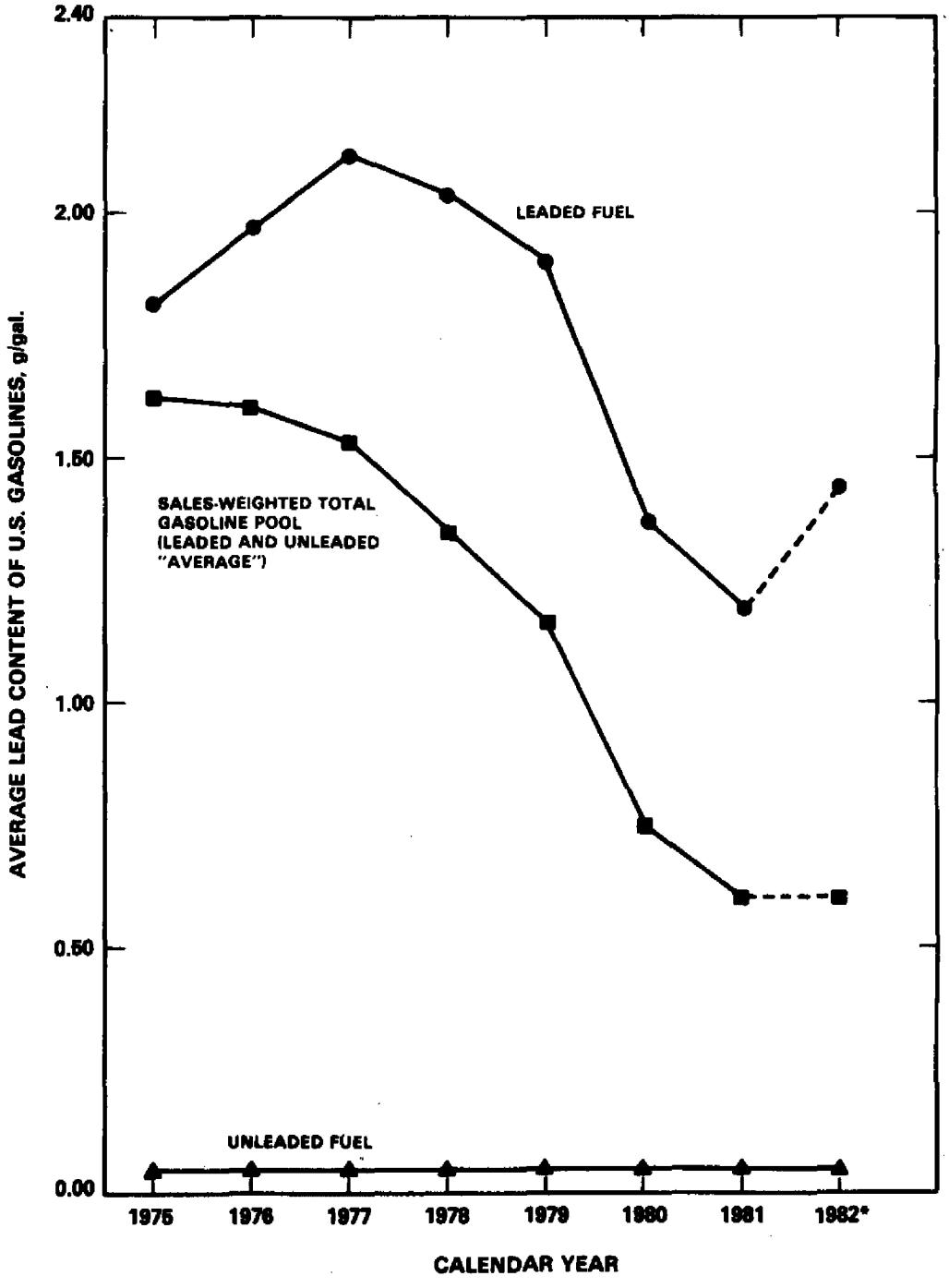

Figure 1-7. Trend in lead content of U.S. gasolines, 1975-1982. (DuPont, 1982).

***1982 DATA ARE FORECASTS.**

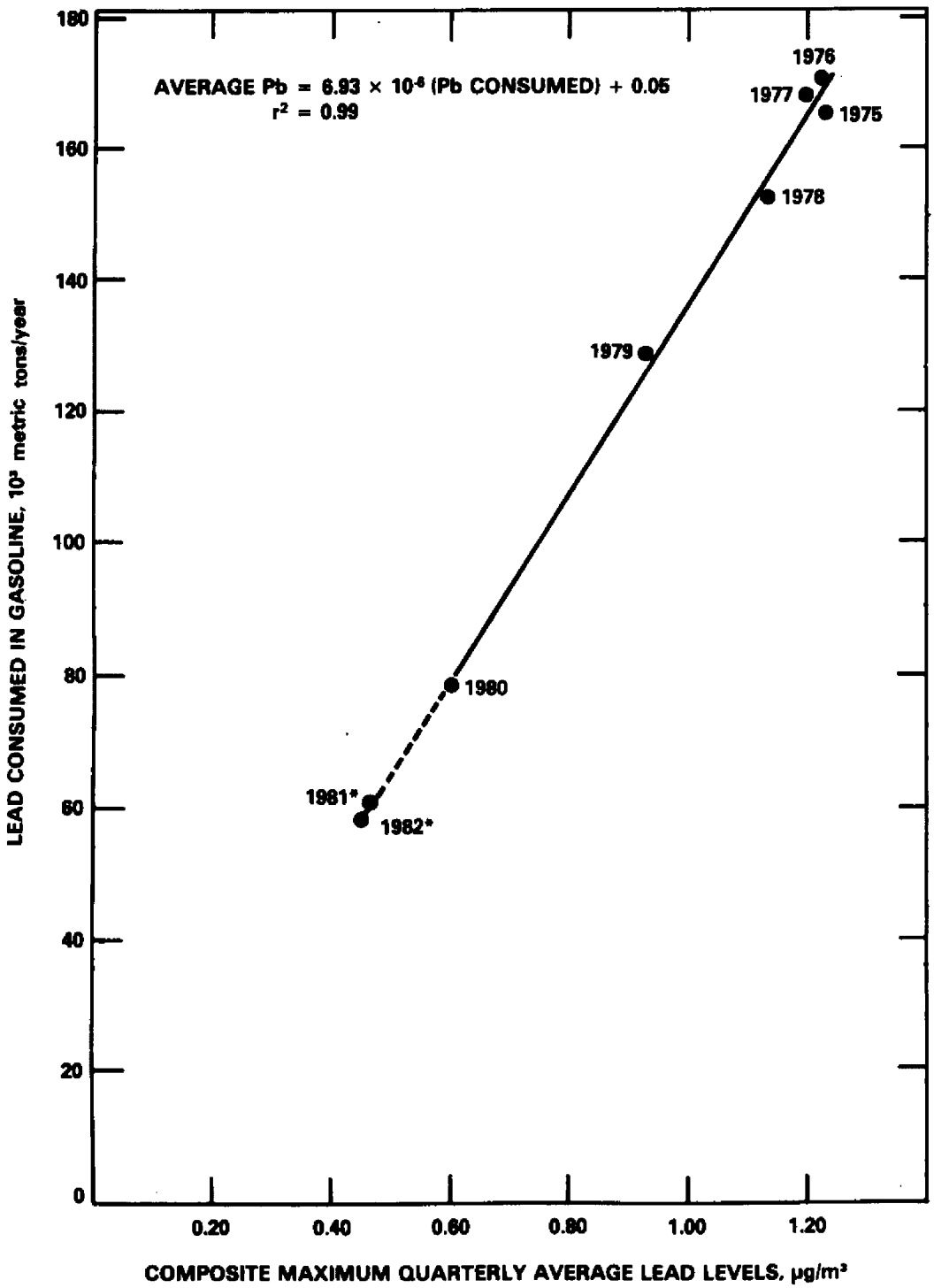

Figure 1-8. Relationship between lead consumed in gasoline and composite maximum quarterly average lead levels, 1975-1980.

*1981 AND 1982 DATA ARE ESTIMATES.

Solid waste incineration and combustion of waste oil are principal contributors of lead emissions from stationary sources. The manufacture of consumer products such as lead glass, storage batteries, and lead additives for gasoline also contributes significantly to stationary source lead emissions. Since 1970, the quantity of lead emitted from the metallurgical industry has decreased somewhat because of the application of control equipment and the closing of several plants, particularly in the zinc and pyrometallurgical industries.

A new locus for lead emissions emerged in the mid-1960s with the opening of the "Viburnum Trend" or "New Lead Belt" in southeastern Missouri. The presence of ten mines and three accompanying lead smelters in this area makes it the largest lead-producing district in the world.

There is no doubt that atmospheric lead has been a component of the human environment since the earliest written record of civilization. Atmospheric emissions are recorded in glacial ice strata and pond and lake sediments. The history of global emissions seems closely tied to production of lead by industrially oriented civilizations. Although the amount of lead to the atmosphere emitted from natural sources is a subject of controversy, even the most liberal estimate (25×10^3 t/year) is dwarfed by the global emissions from anthropogenic sources (450×10^3 t/year). The contribution of gasoline lead to total atmospheric emissions has remained high, at 85 percent, as emissions from stationary sources have decreased at the same pace as from mobile sources. The decrease in stationary source emissions is due primarily to control of stack emissions, whereas the decrease in mobile source emissions is a result of switchover to unleaded gasolines. Production of lead in the United States has remained steady at about 1.2×10^6 t/year for the past decade. The gasoline additive share of this market has dropped from 18 to 9.5 percent during the period 1971 to 1981. The decreasing use of lead in gasoline is projected to continue through 1990.

1.6 TRANSPORT AND TRANSFORMATION

At any particular location and time, the concentration of lead found in the atmosphere depends on the proximity to the source, the amount of lead emitted from sources, and the degree of mixing provided by the motion of the atmosphere. At the source, lead emissions are typically around 10,000 $\mu g/m^3$, while lead values in city air are usually between 0.1 and 10 $\mu g/m^3$. These reduced concentrations are the result of dilution of effluent gas with clean air and the removal of particles by wet or dry deposition. Characteristically, lead concentrations are highest in confined areas close to sources and are progressively reduced by dilution or deposition in districts more removed from sources. In parking garages or tunnels, atmospheric lead concentrations can be ten to a thousand times greater than values measured near roadways or in urban areas. In turn, atmospheric lead concentrations are usually about 2½

times greater in the central city than in residential suburbs. Rural areas have even lower concentrations. Particle size distribution stabilizes within a few hundred kilometers of the sources, although atmospheric concentration continues to decrease with distance. Ambient organolead concentrations decrease more rapidly than inorganic lead, suggesting conversion from the organic to the inorganic phase during transport. Inorganic lead appears to convert from lead halides and oxides to lead sulfates.

Lead is removed from the atmosphere by wet or dry deposition. The mechanisms of dry deposition have been incorporated into models that estimate the flux of atmospheric lead to the earth's surface. Of particular interest is deposition on vegetation surfaces, since this lead may be incorporated into food chains. Between wet and dry deposition, it is possible to calculate an atmospheric lead budget that balances the emission inputs with deposition outputs.

Particles in air streams are subject to the same principles of fluid mechanics as particles in flowing water. The first principle is that of diffusion along a concentration gradient. If the airflow is steady and free of turbulence, the rate of mixing is determined by the diffusivity of the pollutant. By making generalizations of windspeed, stability, and surface roughness, it is possible to construct models using a variable transport factor called eddy diffusivity (K), in which K varies in each direction, including vertically. There is a family of K-theory models that describe the dispersion of particulate pollutants. The simplest K-theory model produces a Gaussian plume, called such because the concentration of the pollutant decreases according to a normal or Gaussian distribution in both the vertical and horizontal directions. These models have some utility and are the basis for most of the air quality simulations performed to date (Benarie, 1980). Another family of models is based on the conservative volume element approach, where volumes of air are seen as discrete parcels having conservative meteorological properties, (Benarie, 1980). The effect of pollutants on these parcels is expressed as a mixing ratio. These parcels of air may be considered to move along a trajectory that follows the advective wind direction. None of the models have been tested for lead. All of the models require sampling periods of two hours or less in order for the sample to conform to a well-defined set of meteorological conditions. In most cases, such a sample would be below the detection limits for lead. The common pollutant used to test models is SO_2 which can be measured over very short, nearly instantaneous, time periods. The question of whether gaseous SO_2 can be used as a surrogate for particulate lead in these models remains to be answered.

Dispersion not influenced by complex terrain features depends on emission rates and the volume of clean air available for mixing. These factors are relatively easy to estimate and some effort has been made to describe ambient lead concentrations which can result under selected conditions. On an urban scale, the routes of transport can be inferred from an isopleth, i.e., a plot connecting points of identical ambient concentrations. These plots always show that lead concentrations are maximum where traffic density is highest.

Dispersion beyond cities to regional and remote locations is complicated by the fact that there are no monitoring network data from which to construct isopleths, that removal by deposition plays a more important role with time and distance, and that emissions from many different geographic locations sources converge. Dispersion from point sources such as smelters and refineries is described with isopleths in the manner of urban dispersion, although the available data are notably less abundant.

Trijonis et al. (1980) reported lead concentrations for seven sites in St. Louis, Missouri. Values around the CBD are typically two to three times greater than those found in the outlying suburbs in St. Louis County to the west of the city. The general picture is one of peak concentrations within congested commercial districts which gradually decline in outlying areas. However, concentration gradients are not steep, and the whole urban area has levels of lead above 0.5 $\mu g/m^3$. Lead in the air decreases 2½-fold from maximum values in center city areas to well populated suburbs, with a further 2-fold decrease in the outlying areas. These modeling estimates are generally confirmed by measurement.

The 15 mines and 7 primary smelters and refineries shown in Figure 1-6 are not located in urban areas. Most of the 56 secondary smelters and refineries are likewise non-urban. Consequently, dispersion from these point sources should be considered separately, but in a manner similar to the treatment of urban regions. In addition to lead concentrations in air, concentrations in soil and on vegetation surfaces are often used to determine the extent of dispersion away from smelters and refineries.

Beyond the immediate vicinity of urban areas and smelter sites, lead in air declines rapidly to concentrations of 0.1 to 0.5 $\mu g/m^3$. Two mechanisms responsible for this change are dilution with clean air and removal by deposition.

Source reconciliation is based on the concept that each type of natural or anthropogenic emission has a unique combination of elemental concentrations. Measurements of ambient air, properly weighted during multivariate regression analysis, should reflect the relative amount of pollutant derived from each of several sources (Stolzenberg et al., 1982). Sievering et al. (1980) used the method of Stolzenberg et al. (1982) to analyze the transport of urban air from Chicago over Lake Michigan. They found that 95 percent of the lead in Lake Michigan air could be attributed to various anthropogenic sources, namely coal fly ash, cement manufacture, iron and steel manufacture, agricultural soil dust, construction soil dust, and incineration emissions. Cass and McRae (1983) used source reconciliation in the Los Angeles Basin to interpret 1976 NFAN data based on emission profiles from several sources. Their chemical element balance model showed that 20 to 22 percent of the total suspended particle mass could be attributed to highway sources.

Harrison and Williams (1982) determined air concentrations, particle size distributions, and total deposition flux at one urban and two rural sites in England. The urban site, which

had no apparent industrial, commercial or municipal emission sources, had an air lead concentration of 3.8 $\mu g/m^3$, whereas the two rural sites were about 0.15 $\mu g/m^3$. The average particle size became smaller toward the rural sites, as the MMED shifted downward from 0.5 μm to 0.1 μm.

Knowledge of lead concentrations in the oceans and glaciers provides some insight into the degrees of atmospheric mixing and long range transport. Patterson and co-workers have measured dissolved lead concentrations in sea water off the coast of California, in the Central North Atlantic (near Bermuda), and in the Mediterranean. The profile obtained by Schaule and Patterson (1980) is shown in Figure 1-9. Surface concentrations in the Pacific (14 ng/kg) were found to be higher than those of the Mediterranean or the Atlantic, decreasing abruptly with depth to a relatively constant level of 1 to 2 ng/kg. The vertical gradient was found to be much less in the Atlantic. Below the mixing layer, there appears to be no difference between lead concentrations in the Atlantic and Pacific. These investigators calculated that industrial lead currently is being added to the oceans at about 10 times the rate of introduction by natural weathering, with significant amounts being removed from the atmosphere by wet and dry deposition directly into the ocean. Their data suggest considerable contamination of surface waters near shore, diminishing toward the open ocean.

Investigations of trace metal concentrations (including lead) in the atmosphere in remote northern and southern hemispheric sites have revealed that the natural sources for such atmospheric trace metals include the oceans and the weathering of the earth's crust, while the major anthropogenic source is particulate air pollution. Enrichment factors for concentrations relative to standard values for the oceans and the crust were calculated; ninety percent of the particulate pollutants in the global troposphere are injected in the northern hemisphere (Robinson and Robbins, 1971). Since the residence times for particles in the troposphere are much less than the interhemispheric mixing time, it is unlikely that significant amounts of particulate pollutants can migrate from the northern to the southern hemisphere via the troposphere.

Murozumi et al. (1969) have shown that long range transport of lead particles emitted from automobiles has significantly polluted the polar glaciers. They collected samples of snow and ice from Greenland and the Antarctic (Figure 1-10). The authors attribute the gradient increase after 1750 to the Industrial Revolution and the accelerated increase after 1940 to the increased use of lead alkyls in gasoline. The most recent levels found in the Antarctic snows were, however, less than those found in Greenland by a factor of 10 or more.

Evidence from remote areas of the world suggests that lead and other fine particle components are transported substantial distances, up to thousands of kilometers, by general weather systems. The degree of surface contamination of remote areas with lead depends both on weather influences and on the degree of air contamination. However, even in remote areas, man's primitive activities can play an important role in atmospheric lead levels.

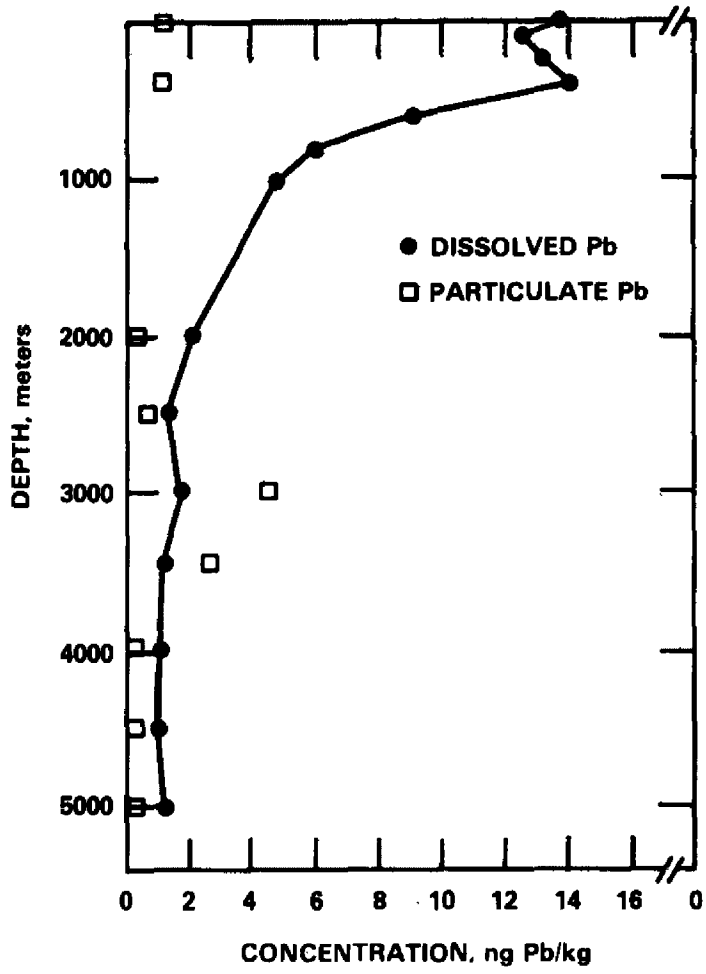

Figure 1-9. Profile of lead concentrations in the central northeast Pacific. Values below 1000 m are an order of magnitude lower than reported by Tatsumoto and Patterson (1963) and Chow and Patterson (1966).

Source: Schaule and Patterson (1980).

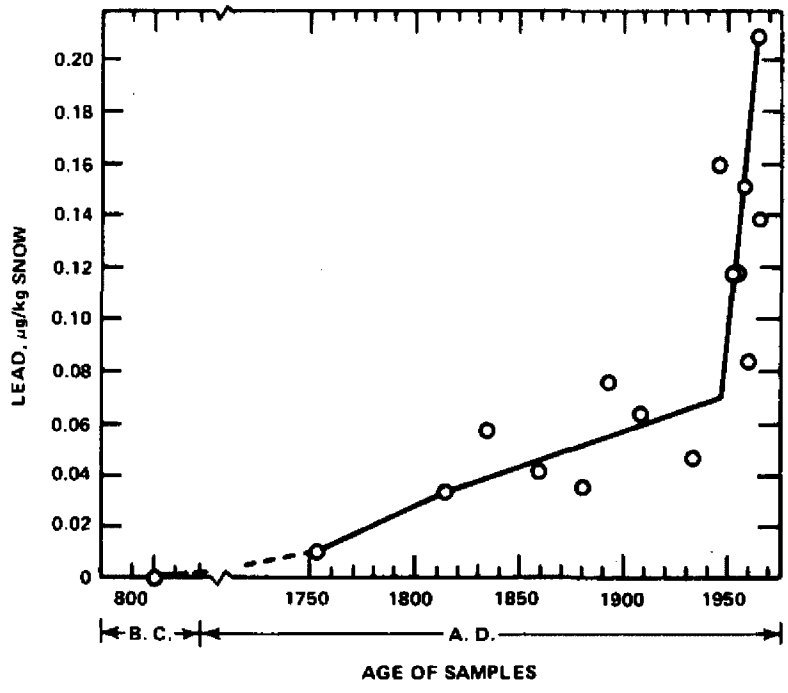

Figure 1-10. Lead concentration profile in snow strata of Northern Greenland.

Source: Murozumi et al. (1969).

Whitby et al. (1975) placed atmospheric particles into three different size regimes: the nuclei mode (<0.1 µm), the accumulation mode (0.1 to 2 µm), and the large particle mode (>2 µm). At the source, lead particles are generally in the nuclei and large particle modes. Large particles are removed by deposition close to the source and particles in the nuclei mode diffuse to surfaces or agglomerate while airborne to form larger particles of the accumulation mode. Thus it is in the accumulation mode that particles are dispersed great distances.

A number of studies have used gas absorbers behind filters to trap vapor-phase lead compounds. Because it is not clear that all the lead captured in the backup traps is, in fact, in the vapor phase in the atmosphere, "organic" or "vapor phase" lead is an operational definition in these studies. Purdue et al. (1973) measured both particulate and organic lead in atmospheric samples. They found that the vapor phase lead was about 5 percent of the total lead in most samples. It is noteworthy, however, that in an underground garage, total lead concentrations were approximately five times those in ambient urban atmospheres, and the organic lead increased to approximately 17 percent.

Lead is emitted into the air from automobiles as lead halides and as double salts with ammonium halides (e.g., $PbBrCl \cdot 2NH_4Cl$). From mines and smelters, $PbSO_4$, $PbO \cdot PbSO_4$, and PbS appear to be the dominant species. In the atmosphere, lead is present mainly as the sulfate

with minor amounts of halides. It is not completely clear just how the chemical composition changes in transport.

The ratio of Br to Pb is often cited as an indication of automotive emissions. From the mixtures commonly used in gasoline additives, the mass Br/Pb ratio should be about 0.386 if there has been no fractionation of either element (Harrison and Sturges, 1983). However, several authors have reported loss of halide, preferentially bromine, from lead salts in atmospheric transport. Both photochemical decomposition and acidic gas displacement have been postulated as mechanisms. The Br/Pb ratios maybe only crude estimates of automobile emissions; this ratio would decrease with distance from the highway from 0.39 to 0.35 at less proximate sites and 0.25 in suburban residential areas. Habibi et al. (1970) studied the composition of auto exhaust particles as a function of particle size. Their main conclusions follow:

1. Chemical composition of emitted exhaust particles is related to particle size.

2. There is considerably more soot and carbonaceous material associated with fine-mode particles than with coarse-mode particles. Particulate matter emitted under typical driving conditions is rich in carbonaceous material.

3. Only small quantities of $2PbBrCl \cdot NH_4Cl$ were found in samples collected at the tailpipe from the hot exhaust gas. Lead-halogen molar ratios in particles of less than 10 μm MMED indicate that much more halogen is associated with these solids than the amount expected from the presence of $2PbBrCl \cdot NH_4Cl$.

Lead sulfide is the main constituent of samples associated with ore handling and fugitive dust from open mounds of ore concentrate. The major constituents from sintering and blast furnace operations appeared to be $PbSO_4$ and $PbO \cdot PbSO_4$, respectively.

Before atmospheric lead can have any effect on organisms or ecosystems, it must be transferred from the air to a surface. For natural ground surfaces and vegetation, this process may be either dry or wet deposition. Transfer by dry deposition requires that the particle move from the main airstream through the boundary layer to a surface. The boundary layer is defined as the region of minimal air flow immediately adjacent to that surface. The thickness of the boundary layer depends mostly on the windspeed and roughness of the surface. Airborne particles do not follow a smooth, straight path in the airstream. On the contrary, the path of a particle may be affected by micro-turbulent air currents, gravitation, or its own inertia. There are several mechanisms which alter the particle path sufficient to cause transfer to a surface. These mechanisms are a function of particle size, windspeed, and surface characteristics. Transfer from the main airstream to the boundary layer is usually by sedimentation or wind eddy diffusion. From the boundary layer to the surface, transfer may be by any of the six mechanisms, although those which are independent of windspeed (sedimentation, interception, Brownian diffusion) are more likely.

Particles transported to a surface by any mechanism are said to have an effective deposition velocity (V_d) which is measured not by rate of particle movement but by accumulation on a surface as a function of air concentration. Several recent models of dry deposition have evolved from the theoretical discussion of Fuchs (1964) and the wind tunnel experiments of Chamberlain (1966). The models of Slinn (1982) and Davidson et al. (1982) are particularly useful for lead deposition. Slinn's model considers a multitude of vegetation parameters to find several approximate solutions for particles in the size range of 0.1 to 1.0 μm, estimating deposition velocities of 0.01 to 0.1 cm/sec. The model of Davidson et al. (1982) is based on detailed vegetation measurements and wind data to predict a V_d of 0.05 to 1.0 cm/sec. Deposition velocities are specific for each vegetation type. Both models show a decrease in deposition velocity as particle size decrease down to about 0.1 to 0.2 μm; as diameter decreases further from 0.1 to 0.001 μm, deposition velocity increases (see Figure 6-1).

Several investigators have used surrogate surface devices to measure dry deposition rates. The few studies available on deposition to vegetation surfaces show deposition rates comparable to those of surrogate surfaces and deposition velocities in the range predicted by the models discussed above (Table 1-2). These data show that global emissions are in approximate balance with global deposition.

Andren et al. (1975) evaluated the contribution of wet and dry deposition of lead in a study of the Walker Branch Watershed in Oak Ridge, Tennessee, during the period June, 1973 - July, 1974. The mean precipitation in the area is approximately 130 cm/yr. Wet deposition contributed approximately 67 percent of the total deposition for the period.

The geochemical mass balance of lead in the atmosphere may be determined from quantitative estimates of inputs and outputs. Inputs amount to 450,000 - 475,000 metric tons annually (Table 1-1). The amount of lead removed by wet deposition is approximately 208,000 t/yr (Table 1-3).

The deposition flux for each vegetation type shown on Table 1-3 totals 202,000. The combined wet and dry deposition is 410,000 metric tons, which compares favorably with the estimated 450,000 - 475,000 metric tons of emissions.

Soils have both a liquid and solid phase, and trace metals are normally distributed between these two phases. In the liquid phase, metals may exist as free ions or as soluble complexes with organic or inorganic ligands. Organic ligands are typically humic substances such as fulvic or humic acid, and the inorganic ligands may be iron or manganese hydrous oxides. Since lead rarely occurs as a free ion in the liquid phase (Camerlynck and Kiekens, 1982), its mobility in the soil solution depends on the availability of organic or inorganic ligands. The liquid phase of soil often exists as a thin film of moisture in intimate contact with the solid phase. The availability of metals to plants depends on the equilibrium between the liquid and solid phase. In the solid phase, metals may be incorporated into crystalline

TABLE 1-2. SUMMARY OF SURROGATE AND VEGETATION SURFACE DEPOSITION OF LEAD

Depositional Surface	Flux ng Pb/cm^2/day	Air Conc ng/m^3	Deposition Velocity cm/sec	Reference
Tree leaves (Paris)	0.38	---	0.086	1
Tree leaves (Tennessee)	0.29-1.2	---	---	2
Plastic disk (remote California)	0.02-0.08	13-31	0.05-0.4	3
Plastic plates (Tennessee)	0.29-1.5	110	0.05-0.06	4
Tree leaves (Tennessee)	---	110	0.005	4
Snow (Greenland)	0.004	0.1-0.2	0.1	5
Grass (Pennsylvania)	---	590	0.2-1.1	6
Coniferous forest (Sweden)	0.74	21 -	0.41	7

1. Servant, 1975
2. Lindberg et al., 1982
3. Elias and Davidson, 1980
4. Lindberg and Harriss, 1981
5. Davidson et al., 1981c
6. Davidson et al., 1982
7. Lannefors et al., 1983

minerals of parent rock material and secondary clay minerals or precipitated as insoluble organic or inorganic complexes. They may also be adsorbed onto the surfaces of any of these solid forms. Of these categories, the most mobile form is in soil moisture, where lead can move freely into plant roots or soil microorganisms with dissolved nutrients. The least mobile is parent rock material, where lead may be bound within crystalline structures over geologic periods of time; intermediate are the lead complexes and precipitates. Transformation from one form to another depends on the chemical environment of the soil. The water soluble and exchangeable forms of metals are generally considered available for plant uptake (Camerlynck and Kiekens, 1982). These authors demonstrated that in normal soils, only a small fraction of the total lead is in exchangeable form (about 1 µg/g) and none exists as free lead ions. Of the exchangeable lead, 30 percent existed as stable complexes, 70 percent as labile complexes.

TABLE 1-3. ESTIMATED GLOBAL DEPOSITION OF ATMOSPHERIC LEAD

	Deposition from Atmosphere		
	Mass 10^{17} kg/yr	Concentration 10^{-6} g/kg	Deposition 10^{6} kg/yr
Wet			
To oceans	4.1	0.4	164
To continents	1.1	0.4	44
Dry	Area 10^{12} km^2	Deposition rate 10^{-3} g/m^2/yr	Deposition 10^{6} kg/yr
To oceans, ice caps, deserts	405	0.2	89
Grassland, agricultural areas, and tundra	46	0.71	33
Forests	59	1.5	80
		Total dry:	202
		Total wet:	208
		Global:	410

Source: This report.

Atmospheric lead may enter the soil system by wet or dry deposition mechanisms. Lead could be immobilized by precipitation as less soluble compounds [$PbCO_3$, $Pb(PO_4)_2$], by ion exchange with hydrous oxides or clays, or by chelation with humic and fulvic acids. Lead immobilization is more strongly correlated with organic chelation than with iron and managanese oxide formation (Zimdahl and Skogerboe, 1977). If organic chelation is the correct model of lead immobilization in soil, then several features of this model merit further discussion. First, the total capacity of soil to immobilize lead can be predicted from the linear relationship developed by Zimdahl and Skogerboe (1977) (Figure 1-11) based on the equation:

$$N = 2.8 \times 10^{-6} (A) + 1.1 \times 10^{-5} (B) - 4.9 \times 10^{-5}$$

where N is the saturation capacity of the soil expressed in moles/g soil, A is the cation exchange capacity of the soil in meq/100 g soil, and B is the pH.

The soil humus model also facilitates the calculation of lead in soil moisture using values available in the literature for conditional stability constants (K) with fulvic acid. The values reported for log K are linear in the pH range of 3 to 6 so that interpolations in the critical range of pH 4 to 5.5 are possible (Figure 1-11). Thus, at pH 4.5, the ratio of complexed lead to ionic lead is expected to be 3.8×10^3. For soils of 100 µg/g, the ionic lead in soil moisture solution would be 0.03 µg/g.

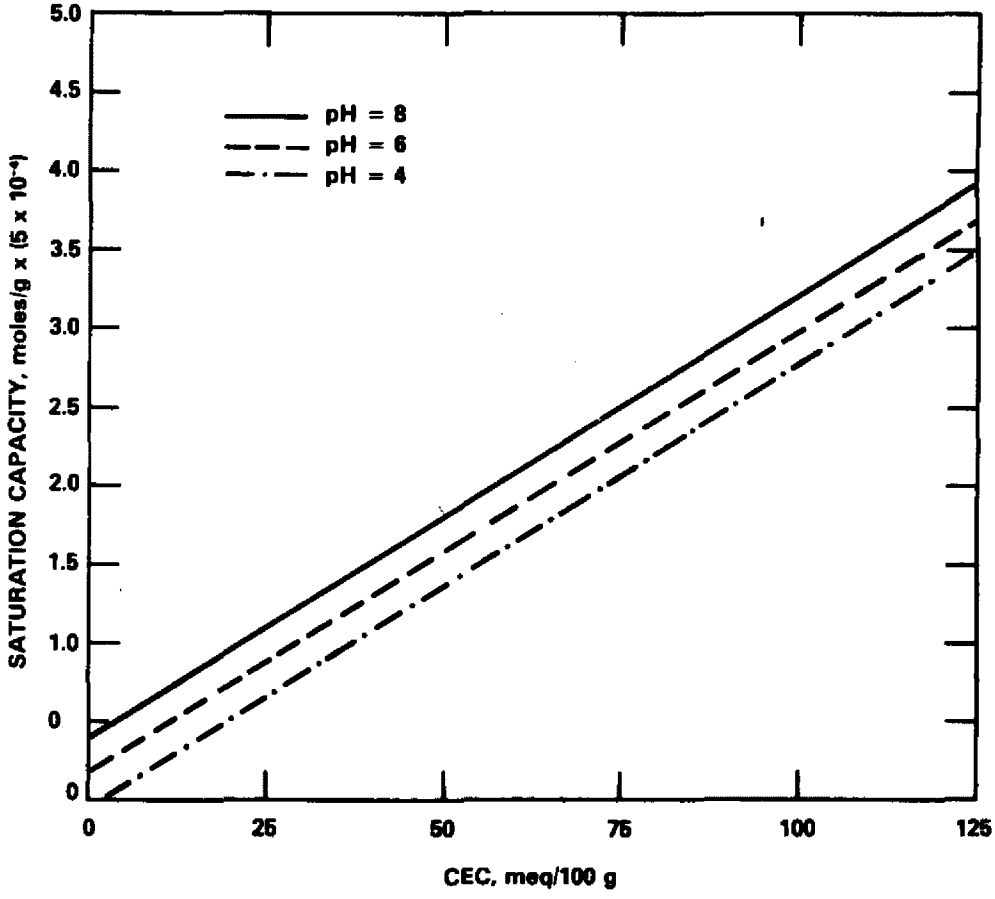

Figure 1-11. Variation of lead saturation capacity with cation exchange capacity in soil at selected pH values.

Source: Data from Zimdahl and Skogerboe (1977).

It is also important to consider the stability constant of the Pb-FA complex relative to other metals. Schnitzer and Hansen (1970) showed that at pH 3, Fe^{3+} is the most stable in the sequence $Fe^{3+} > Al^{3+} > Cu^{2+} > Ni^{2+} > Co^{2+} > Pb^{2+} > Ca^{2+} > Zn^{2+} > Mn^{2+} > Mg^{2+}$. At pH 5, this sequence becomes $Ni^{2+} = Co^{2+} > Pb^{2+} > Cu^{2+} > Zn^{2+} = Mn^{2+} > Ca^{2+} > Mg^{2+}$. This means that at normal soil pH levels of 4.5 to 8, lead is bound to FA + HA in preference to many other metals that are known plant nutrients (Zn, Mn, Ca, and Mg).

Lead does not pass easily to ground or surface water. Any lead dissolved from primary lead sulfide ore tends to combine with carbonate or sulfate ions to form insoluble lead carbonate or lead sulfate, or be absorbed by ferric hydroxide. An outstanding characteristic of lead is its tendency to form compounds of low solubility with the major anions of natural water. The hydroxide, carbonate, sulfide, and more rarely the sulfate may act as solubility controls in precipitating lead from water. The amount of lead that can remain in solution is a function of the pH of the water and the dissolved salt content. A significant fraction of the lead carried by river water may be in an undissolved state. This insoluble lead can consist of colloidal particles in suspension or larger undissolved particles of lead carbonate, -oxide, -hydroxide, or other lead compounds incorporated in other components of particulate lead from runoff; it may occur either as sorbed ions or surface coatings on sediment mineral particles or be carried as a part of suspended living or nonliving organic matter.

The bulk of organic compounds in surface waters originates from natural sources. (Neubecker and Allen, 1983). The humic and fulvic acids that are primary complexing agents in soils are also found in surface waters at concentrations from 1 to 5 mg/l, occasionally exceeding 10 mg/l. The presence of fulvic acid in water has been shown to increase the rate of solution of lead sulfide 10 to 60 times over that of a water solution at the same pH that did not contain fulvic acid. At pH values near 7, soluble lead-fulvic acid complexes are present in solution.

The transformation of inorganic lead, especially in sediment, to tetramethyllead (TML) has been observed and biomethylation has been postulated. However, Reisinger et al. (1981) have reported extensive studies of the methylation of lead in the presence of numerous bacterial species known to alkylate mercury and other heavy metals. In these experiments no biological methylation of lead was found under any condition.

Lead occurs in riverine and estuarial waters and alluvial deposits. Concentrations of lead in ground water appear to decrease logarithmically with distance from a roadway. Rainwater runoff has been found to be an important transport mechanism in the removal of lead from a roadway surface in a number of studies. Apparently, only a light rainfall, 2 to 3 mm, is sufficient to remove 90 percent of the lead from the road surface to surrounding soil and to waterways. The lead concentrations in off-shore sediments often show a marked increase corresponding to anthropogenic activity in the region. An average anthropogenic flux of 72 $mg/m^2 \cdot yr$, of which 27 $mg/m^2 \cdot yr$ could be attributed to direct atmospheric deposition. Prior to 1650, the total flux was 12 $mg/m^2 \cdot yr$, so there has been a 6-fold increase since that time. Ng and Patterson (1982) found prehistoric fluxes of 1 to 7 mg $Pb/m^2 \cdot yr$ to three offshore basins in southern California, which have now increased 3 to 9-fold to 11 to 21 $mg/m^2 \cdot yr$. Much of this lead is deposited directly from sewage outfalls, although at least 25 percent probably comes from the atmosphere.

The deposition of lead on the leaf surfaces of plants where the particles are often retained for a long time can be important. Several studies have shown that plants near roadways exhibit considerably higher levels of lead than those farther away. Rainfall does not generally remove the deposited particles. Animals or humans consuming the leafy portions of such plants can be exposed to higher than normal levels of lead. The particle deposition on leaves has led some investigators to stipulate that lead may enter plants through the leaves. Arvik and Zimdahl (1974) have shown that entry of ionic lead through plant leaves is of minimal importance. Using the leaf cuticles of several types of plants essentially as dialysing membranes, they found that even high concentrations of lead ions would not pass through the cuticles into distilled water on the opposite side.

1.7 ENVIRONMENTAL CONCENTRATIONS AND POTENTIAL PATHWAYS TO HUMAN EXPOSURE

In general, typical levels of human lead exposure may be attributed to four components of the human environment: inhaled air, dusts of various types, food and drinking water. A baseline level of potential human exposure is determined for a normal adult eating a typical diet and living in a non-urban community. This baseline exposure is deemed to be unavoidable by any reasonable means. Beyond this level, additive exposure factors can be determined for other environments (urban, occupational, smelter communities), for certain habits and activities (smoking, drinking, pica, and hobbies), and for variations due to age, sex, or socioeconomic status.

1.7.1 Lead in Air

Ambient airborne lead concentrations may influence human exposure through direct inhalation of lead-containing particles and through ingestion of lead which has been deposited from the air onto surfaces. Our understanding of the pathways to human exposure is far from complete because most ambient measurements were not taken in conjuction with studies of the concentrations of lead in man or in components of his food chain.

The most complete set of data on ambient air concentrations may be extracted from the National Filter Analysis Network (NFAN) and its predecessors. In remote regions of the world, air concentrations are two or three orders of magnitude lower than in urban areas, lending credence to estimates of the concentrations of natural lead in the atmosphere. In the context of this data base, the conditions which modify ambient air, as measured by the monitoring networks, to air inhaled by humans cause changes in particle size distributions, changes with vertical distance above ground, and differences between indoor and outdoor concentrations.

The wide range of concentration is apparent from Table 1-4, which summarizes data obtained from numerous independent measurements. Concentrations vary from 0.000076 $\mu g/m^3$ in

TABLE 1-4. ATMOSPHERIC LEAD IN URBAN, RURAL, AND REMOTE AREAS OF THE WORLD[a]

Location	Sampling Period	Lead conc. ($\mu g/m^3$)	Reference
Urban			
Miami	1974	1.3	HASL, 1975
New York	1978-79	1.1	see Table 7-3
Boston	1978-79	0.8	see Table 7-3
St. Louis	1973	1.1	see Table 7-3
Houston	1978-79	0.9	see Table 7-3
Chicago	1979	0.8	see Table 7-3
Salt Lake City	1974	0.89	HASL, 1975
Los Angeles	1978-79	1.4	see Table 7-3
Ottowa	1975	1.3	NAPS, 1975
Toronto	1975	1.3	NAPS, 1975
Montreal	1975	2.0	NAPS, 1975
Berlin	1966-67	3.8	Blokker, 1972
Vienna	1970	2.9	Hartl and Resch, 1973
Zurich	1970	3.8	Högger, 1973
Brussels	1978	0.5	Roels et al., 1980
Turin	1974-79	4.5	Facchetti and Geiss, 1982
Rome	1972-73	4.5	Colacino and Lavagnini, 1974
Paris	1964	4.6	Blokker, 1972
Rio de Janeiro	1972-73	0.8	Branquinho and Robinson, 1976
Rural			
New York Bight	1974	0.13	Duce et al., 1975
Framingham, MA	1972	0.9	O'Brien et al., 1975
Chadron, NE	1973-74	0.045	Struempler, 1975
United Kingdom	1972	0.13	Cawse, 1974
Italy	1976-80	0.33	Facchetti and Geiss, 1982
Belgium	1978	0.37	Roels et al. 1980
Remote			
White Mtn., CA	1969-70	0.008	Chow et al., 1972
High Sierra, CA	1976-77	0.021	Elias and Davidson, 1980
Olympic Nat. Park, WA	1980	0.0022	Davidson et al., 1982
Antarctica	1971	0.0004	Duce, 1972
South Pole	1974	0.000076	Maenhaut et al., 1979
Thule, Greenland	1965	0.0005	Murozumi et al., 1969
Thule, Greenland	1978-79	0.008	Heidam, 1981
Prins Christian-sund, Greenland	1978-79	0.018	Heidam, 1981
Dye 3, Greenland	1979	0.00015	Davidson et al., 1981c
Eniwetok, Pacific Ocean	1979	0.00017	Settle and Patterson, 1982
Kumjung, Nepal	1979	0.00086	Davidson et al., 1981b
Bermuda	1973-75	0.0041	Duce et al., 1976
Spitsbergen	1973-74	0.0058	Larssen, 1977

[a]All references listed as cited in Nriagu (1978b).

remote areas to over 10 $\mu g/m^3$ near sources such as smelters. Many of the remote areas are far from human habitation and therefore do not reflect human exposure. However, a few of the regions characterized by small lead concentrations are populated by individuals with primitive lifestyles; these data provide baseline airborne lead data to which modern American lead exposures can be compared.

The remote area concentrations reported in Table 1-4 do not necessarily reflect natural, preindustrial lead. Murozumi et al. (1969) and Ng and Patterson (1981) have measured a 200-fold increase in the lead content of Greenland snow over the past 3000 years. The authors state that this lead originates in populated mid-latitude regions, and is transported over thousands of kilometers through the atmosphere to the Arctic. All of the concentrations in Table 1-4, including values for remote areas, have been influenced by anthropogenic lead emissions.

The data from the Air Filter networks show both the maximum quarterly average to reflect compliance of the station to the ambient airborne standard (1.5 $\mu g/m^3$), and quarterly averages to show trends at a particular location. The number of stations complying with the standard has increased, the quarterly averages have decreased, and the maximum 24-hour values appear to be smaller since 1977.

It seems likely that the concentration of natural lead in the atmosphere is between 0.00002 and 0.00007 $\mu g/m^3$. A value of 0.00005 will be used for calculations regarding the contribution of natural air lead to total human uptake.

The effect of the 1978 National Ambient Air Quality Standard for Lead has been to reduce the air concentration of lead in major urban areas. Similar trends may also be seen in urban areas of smaller population density. There are many factors which can cause differences between the concentration of lead measured at a monitoring station and the actual inhalation of air by humans. Air lead concentrations usually decrease with vertical and horizontal distance from emission sources, and are generally lower indoors than outdoors.

New guidelines for placing ambient air lead monitors went into effect in July, 1981 (F.R., 1981 September 3). "Microscale" sites, placed between 5 and 15 meters from thoroughfares and 2 to 7 meters above the ground, are prescribed, but until now few monitors have been located that close to heavily travelled roadways. Many of these microscale sites might be expected to show higher lead concentrations than measured at nearby middlescale urban sites, due complex. Our understanding of the complex factors affecting the vertical distribution of airborne lead is extremely limited, but the data indicate that air lead concentrations are primarily a function of distance from the source, whether vertical or horizontal.

Because people spend much of their time indoors, ambient air data may not accurately indicate actual exposure to airborne lead. Some studies show smaller indoor/outdoor ratios

during the winter, when windows and doors are tightly closed. Overall, the data suggest indoor/outdoor ratios of 0.6-0.8 are typical for airborne lead in houses without air conditioning. Ratios in air conditioned houses are expected to be in the range of 0.3-0.5 (Yocum, 1982). Even detailed knowledge of indoor and outdoor airborne lead concentrations at fixed locations may still be insufficient to assess human exposure to airborne lead. The study of Tosteson et al. (1982) included measurement of airborne lead concentrations using personal exposure monitors, carried by individuals going about their day-to-day activities. In contrast to the lead concentrations of 0.092 and 0.12 $\mu g/m^3$ at fixed locations, the average personal exposure was 0.16 $\mu g/m^3$. The authors suggest the inadequacy of using fixed monitors at either indoor or outdoor locations to assess exposure.

Much of the lead in the atmosphere is transferred to terrestrial surfaces where it is eventually passed to the upper layer of the soil surface. Crustal lead concentrations in soil range from less than 10 to greater than 70 $\mu g/g$. The range of values probably represent natural levels of lead in soil, although there may have been some contamination with anthropogenic lead during collection and handling.

1.7.2 Lead in Soil and Dust

Studies have determined that atmospheric lead is retained in the upper two centimeters of undisturbed soil, especially soils with at least 5 percent organic matter and a pH of 5 or above. There has been no general survey of this upper 2 cm of the soil surface in the United States, but several studies of lead in soil near roadsides and smelters and a few studies of lead in soil near old houses with lead-based paint can provide the backgound information for determining potential human exposures to lead from soil. Because lead is immobilized by the organic component of soil, the concentration of anthropogenic lead in the upper 2 cm is determined by the flux of atmospheric lead to the soil surface. Near roadsides, this flux is largely by dry deposition and the rate depends on particle size and concentration. In general, deposition flux drops off abruptly with increasing distance from the roadway. This effect is demonstrated in studies which show surface soil lead decreases exponentially up to 25 m from the edge of the road. Roadside soils may contain atmospheric lead from 30 to 2000 mg/g in excess of natural levels within 25 meters of the roadbed, all in the upper layer of the soil profile.

Near primary and secondary smelters, lead in soil decreases exponentially within a 5-10 km zone around the smelter complex. Soil lead contamination varies with the smelter emission rate, length of time the smelter has been in operation, prevailing windspeed and direction, regional climatic conditions, and local topography.

Urban soils may be contaminated from a variety of atmospheric and non-atmospheric sources. The major sources of soil lead seem to be paint chips from older houses and deposition from nearby highways. Lead in soil adjacent to a house decreases with distance; this may

be due to paint chips or to dust of atmospheric origin washing from the rooftop (Wheeler and Rolfe, 1979).

A definitive study which describes the source of soil lead was reported by Gulson et al. (1981) for soils in the vicinity of Adelaide, South Australia. In an urban to rural transect, stable lead isotopes were measured in the top 10 cm of soils over a 50 km distance. By their isotopic compositions, three sources of lead were identified: natural, non-automotive industrial lead from Australia, and tetraethyl lead manufactured in the United States. The results indicated most of the soil surface lead originated from leaded gasoline. Lead may be found in inorganic primary minerals, on humic substances, complexed with Fe-Mn oxide films, on secondary minerals or in soil moisture. All of the lead in primary minerals is natural and is bound tightly within the crystalline structure of the minerals. The lead on the surface of these minerals is leached slowly into the soil moisture. Atmospheric lead forms complexes with humic substances or on oxide films, that are in equilibrium with soil moisture, although the equilibrium strongly favors the complexing agents. Except near roadsides and smelters, only a few μg of atmospheric lead have been added to each gram of soil. Several studies indicate that this lead is available to plants and that even with small amounts of atmospheric lead, about 75 percent of the lead in soil moisture is of atmospheric origin.

Lead on the surfaces of vegetation may be of atmospheric origin. In internal tissues, lead maybe a combination of atmospheric and soil origin. As with soils, lead on vegetation surfaces decreases exponentially with distance away from roadsides and smelters. This deposited lead is persistent. It is neither washed off by rain nor taken up through the leaf surface. Lead on the surface of leaves and bark is proportional to air lead concentrations and particle size distributions. Lead in internal plant tissues is directly related to lead in soil.

1.7.3 Lead in Food

In a study to determine the background concentrations of lead and other metals in agricultural crops, the Food and Drug Administration (Wolnik et al., 1983), in cooperation with the U.S. Department of Agriculture and the U.S. Environmental Protection Agency, analyzed over 1500 samples of the most common crops taken from a cross section of geographic locations. Collection sites were remote from mobile or stationary sources of lead. Soil lead concentrations were within the normal range (8-25 μg/g) of U.S. soils. The concentrations of lead in crops are shown as "Total" concentrations on Table 1-5. The total concentration data should probably be seen as representing the lowest concentrations of lead in food available to Americans. The data on these ten crops suggest that root vegetables have lead concentrations between 0.0046 and 0.009 μg/g, all soil lead. Aboveground parts not exposed to significant amounts of atmospheric deposition (sweet corn and tomatoes) have less lead internally. If it

is assumed that this same concentration is the internal concentration for aboveground parts for other plants, it is apparent that five crops have direct atmospheric deposition in proportion to surface area and estimated duration of exposure. The deposition rate of 0.04 $ng/cm^2 \cdot day$ in rural environments could account for these amounts of direct atmospheric lead.

TABLE 1-5. BACKGROUND LEAD IN BASIC FOOD CROPS AND MEATS
(µg/g fresh weight)

Crop	Natural Pb	Indirect Atmospheric	Direct Atmospheric	Total†
Wheat	0.0015	0.0015	0.034	0.037
Potatoes	0.0045	0.0045	--	0.009
Field corn	0.0015	0.0015	0.019	0.022*
Sweet corn	0.0015	0.0015	--	0.003
Soybeans	0.021	0.021	--	0.042
Peanuts	0.050	0.050	--	0.100
Onions	0.0023	0.0023	--	0.0046*
Rice	0.0015	0.0015	0.004	0.007*
Carrots	0.0045	0.0045	--	0.009*
Tomatoes	0.001	0.001	--	0.002*
Spinach	0.0015	0.0015	0.042	0.045*
Lettuce	0.0015	0.0015	0.010	0.013
Beef (muscle)	0.0002	0.002	0.02	0.02**
Pork (muscle)	0.0002	0.002	0.06	0.06**

†except as indicated, data are from Wolnick et al. (1983)

*preliminary data provided by the Elemental Analysis Research Center, Food and Drug Administration, Cincinnati, OH

**data from Penumarthy et al. (1980)

Lead in food crops varies according to exposure to the atmosphere and in proportion to the effort taken to separate husks, chaff, and hulls from edible parts during processing for human or animal consumption. Root parts and protected aboveground parts contain natural lead and indirect atmospheric lead, both derived from the soil. For exposed aboveground parts, any lead in excess of the average of unexposed aboveground parts is considered to have been directly deposited from the atmosphere.

1.7.4 Lead in Water

Lead occurs in untreated water in either dissolved or particulate form. Dissolved lead is operationally defined as that which passes through a 0.45 µm membrane filter. Because atmospheric lead in rain or snow is retained by soil, there is little correlation between lead in

precipitation and lead in streams that drain terrestrial watersheds. Rather, the important factors seem to be the chemistry of the stream (pH and hardness) and the volume of the stream flow. For groundwater, chemistry is also important, as is the geochemical composition of the water-bearing bedrock.

Streams and lakes are influenced by their water chemistry and the lead content of their sediments. At neutral pH, lead moves from the dissolved to particulate form and the particles eventually pass to sediments. At low pH, the reverse pathway is generally the case. Hardness, which is a combination of the Ca and Mg concentration, can also influence lead concentrations. At higher concentrations of Ca and Mg, the solubility of lead decreases. Municipal and private wells typically have a neutral pH and somewhat higher than average hardness. Lead concentrations are not influenced by acid rain, surface runoff or atmospheric deposition. Rather, the primary determinant of lead concentration is the geochemical makeup of the bedrock that is the source of the water supply. Ground water typically ranges from 1 to 100 µg Pb/l (National Academy of Sciences, 1980).

Whether from surface or ground water supplies, municipal waters undergo extensive chemical treatment prior to release to the distribution system. Although there is no direct effort to remove lead from the water supply, some treatments, such as flocculation and sedimentation, may inadvertently remove lead along with other undesirable substances. On the other hand, chemical treatment to soften water increases the solubility of lead and enhances the possibility that lead will be added to water as it passes through the distribution system. For samples taken at the household tap, lead concentrations are usually higher in the initial volume (first daily flush) than after the tap has been running for some time. Water standing in the pipes for several hours is intermediate between these two concentrations. (Sharrett et al., 1982; Worth et al., 1981).

1.7.5 Baseline Exposures to Lead

Lead concentrations in environmental media that are in the pathway to human consumption are summarized on Table 1-6. Because natural lead is generally three to four orders of magnitude lower than anthropogenic lead in ambient rural or urban air, all atmospheric contributions of lead are considered to be of anthropogenic origin. Natural soil lead typically ranges from 10 to 30 µg/g, but much of this is tightly bound within the crystalline matrix of soil minerals at normal soil pHs of 4 to 8. Lead in the organic fraction of soil is part natural and part atmospheric. The fraction derived from fertilizer is considered to be minimal. In undisturbed rural and remote soils, the ratio of natural to atmospheric lead is about 1:1, perhaps as high as 1:3. This ratio persists through soil moisture and into internal plant tissues.

TABLE 1-6. SUMMARY OF ENVIRONMENTAL CONCENTRATIONS OF LEAD

Medium	Natural Lead	Atmospheric Lead	Total Lead
Air urban (μg/m3)	0.00005	0.8	0.8
rural (μg/m3)	0.00005	0.2	0.2
Soil Total (μg/g)	8-25	3.0	15.0
Food Crops (μg/g)	0.0025	0.027	0.03
Surface water (μg/g)	0.00002	0.005	0.005
Ground water (μg/g)	0.003	--	0.003

In tracking air lead through pathways to human exposure, it is necessary to distinguish between atmospheric lead that has passed through the soil, called indirect atmospheric here, and atmospheric lead that has deposited directly on crops or water. Because indirect atmospheric lead will remain in the soil for many decades, this source is insensitive to projected changes in atmospheric lead concentrations.

Initially, a current baseline exposure scenario is described for an individual with a minimum amount of daily lead consumption. This person would live and work in a nonurban environment, eat a normal diet of food taken from a typical grocery shelf, and would have no habits or activities that would tend to increase lead exposure. Lead exposure at the baseline level is considered unavoidable without further reductions of lead in the atmosphere or in canned foods. Most of the baseline lead is of anthropogenic origin.

To arrive at a minimum or baseline exposure for humans, it is necessary to begin with the environmental components, air, soil, food crops and water, that are the major sources of lead consumed by humans (Table 1-6). These components are measured frequently, even monitored routinely in the case of air, so that much data are available on their concentrations. But there are several factors which modify these components prior to actual human exposure: We do not breathe air as monitored at an atmospheric sampling station; we may be closer to or farther from the source of lead than is the monitor; we may be inside a building, with or without filtered air; water we drink does not come directly from a stream or river, but often has passed through a chemical treatment plant and a distribution system. A similar type of processing has modified the lead levels present in our food.

Besides the atmospheric lead in environmental components, there are two other industrial components which contribute to this baseline of human exposure: paint pigments and lead

solder. Solder contributes directly to the human diet through canned food and copper water distribution systems. Paint and solder are also a source of lead-bearing dusts. The most common dusts in the baseline human environment are street dusts and household dusts. They originate as emissions from mobile or stationary sources, as the oxidation products of surface exposure, or as products of frictional grinding processes. Dusts are different from soil in that soil derives from crustal rock and typically has a lead concentration of 10 to 30 µg/g, whereas dusts come from both natural and anthropogenic sources and vary from 1000 to 10,000 µg/g.

The route by which many people receive the largest portion of their daily lead intake is via foods. Several studies have reported average dietary lead intakes in the range 100 to 500 µg/day for adults, with individual diets covering a much greater range (Nutrition Foundation, 1982). The sources of lead in plants and animals are air, soil, and untreated waters (Figure 1-13). Food crops and livestock contain lead in varying proportions from the atmosphere and natural sources. From the farm to the dinner table, lead is added to food as it is harvested, transported, processed, packaged, and prepared. The sources of this lead are dusts of atmospheric and industrial origin, metals used in grinding, crushing, and sieving, solder used in packaging, and water used in cooking. Pennington (1983) has identified 234 typical food categories for Americans grouped into eight age/sex groups. These basic diets are the foundation for the Food and Drug Administration's revised Total Diet Study, often called the "Market Basket Study", beginning in April, 1982. The diets used for this discussion include food, beverages, and drinking water for the 2-year-old child, the adult female 25 to 30 years of age, and the adult male 25 to 30 years of age.

Milk and foods are treated separately from water and beverages because solder and atmospheric lead contribute significantly to each of these later dietary components (Figure 1-1).

Between the field and the food processor, lead is added to food crops. It is assumed that this lead is all of direct atmospheric origin. Direct atmospheric lead can be deposited directly on food materials by dry deposition, or it can be lead on dust which has collected on other surfaces, then transferred to foods. For the purposes of this discussion, it is not necessary to distinguish between these two forms, as both are a function of air concentration.

For some of the food items, data are available on lead concentrations just prior to filling of cans. In the case where the food product has not undergone extensive modification (e.g. cooking or added ingredients), the added lead was most likely derived from the atmosphere or from the machinery used to handle the product.

From the time a product is packaged in bottles, cans, or plastic containers until it is opened in the kitchen, it may be assumed that no food item receives atmospheric lead. Most of the lead which is added during this stage comes from the solder used to seal some types of

TABLE 1-7. SUMMARY BY AGE AND SEX OF ESTIMATED AVERAGE LEVELS OF LEAD INGESTED FROM MILK AND FOODS

	Dietary consumption (g/day)				Lead consumption µg/day		
	2-yr-old Child	Adult Female	Adult Male	µg Pb/g*	2-yr-old Child	Adult Female	Adult Male
A. Dairy	381	237	344	0.013	5.0	3.1	4.5
B. Meat	113	169	288	0.036	4.1	6.1	10.4
C. Food crops	260	350	505	0.022	5.7	7.7	11.1
D. Canned food	58	68	82	0.24	13.9	16.3	19.7
Total	812	824	1219		28.7	33.2	45.6

*Weighted average lead concentration in foods from Table 7-15 in Chapter 7 of this document.

cans. Estimates by the Food and Drug Administration, prepared in cooperation with the National Food Processors Association, suggest that lead in solder contributes more than 66 percent of the lead in canned foods where a lead solder side seam was used. This lead is thought to represent a contribution of 20 percent to the total lead consumption in foods.

The contribution of the canning process to overall lead levels in albacore tuna has been reported by Settle and Patterson (1980). The study showed that lead concentrations in canned tuna are elevated above levels in fresh tuna by a factor of 4000. Nearly all of the increase results from leaching of the lead from the soldered seam of the can; tuna from an unsoldered can is elevated by a factor of only 20 compared with tuna fresh from the sea.

It is assumed that no further lead is added to food packaged in plastic or paper containers, although there are no data to support or reject this assumption.

Studies that reflect contributions of lead added during kitchen preparation showed that lead in acidic foods stored refrigerated in open cans can increase by a factor of 2 to 8 in five days if the cans have a lead-soldered side seam not protected by an interior lacquer coating (Capar, 1978). Comparable products in cans with the lacquer coating or in glass jars showed little or no increase.

As a part of its program to reduce the total lead intake by children (0-5 years) to less than 100 µg/day by 1988, the Food and Drug Administration estimated lead intakes for individual children in a large-scale food consumption survey (Beloian and McDowell, 1981). Between 1973 and 1978, intensive efforts were made by the food industry to remove sources lead from infant food items. By 1980, there had been a 47 percent reduction in the age group 0-5 months and a 7 percent reduction for 6-23 months. Most of this reduction was accomplished by the removal of soldered cans used for infant formula.

Because the Food and Drug Administration is actively pursuing programs to remove lead from adult foods, it is probable that there will be a decrease in total dietary lead consumption over the next decade independent of projected decreases in atmospheric lead concentration. With both sources of lead minimized, the lowest reasonable estimated dietary lead consumption would be 10-15 µg/day for adults and children. This estimate assumes about 90 percent of the direct atmospheric, solder lead and lead of undetermined origin would be removed from the diet, leaving 8 µg from these sources and 3 µg of natural and indirect atmospheric lead.

There have been several studies in North America and Europe of the sources of lead in drinking water. The baseline concentration of water across the whole United States is taken to be 10 µg/l, although 6-8 µg/l are often cited in the literature for specific locations. A recent study in Seattle, WA by Sharrett et al. (1982) showed that the age of the house and the type of plumbing determined the lead concentration in tap water. Standing water from houses newer than five years (copper pipes) averaged 31 µg/l, while houses less than 18 months old averaged about 70 µg/l. Houses older than five years and houses with galvanized pipe averaged less than 6 µg/l. The source of the water supply, the length of the pipe, and the use of plastic pipes in the service line had little or no effect on the lead concentrations. It appears certain that the source of lead in new homes with copper pipes is the solder used to join these pipes, and that this lead is eventually worn away with age.

Ingestion, rather than inhalation, of dust particles appears to be the greater problem in the baseline environment, especially ingestion during meals and playtime activity by small children. Although dusts are of complex origin, they may be conveniently placed into a few categories relating to human exposure. Generally, the most convenient categories are household dusts, soil dust, street dusts, and occupational dusts. It is a characteristic of dust particles that they accumulate on exposed surfaces and are trapped in the fibers of clothing and carpets. Two other features of dusts are important. First, they must be described in both concentration and amount; the concentration of lead in street dust may be the same in a rural and urban environment, but the amount of dust may differ by a wide margin. Secondly, each category represents some combination of sources. Household dusts contain some atmospheric lead, some paint lead, and some soil lead; street dusts contain atmospheric, soil, and occasionally paint lead. For the baseline human exposure, it is assumed that workers are not exposed to occupational dusts, nor do they live in houses with interior leaded paints. Street dust, soil dust, and some household dust are the primary sources for baseline potential human exposure.

In considering the impact of street dust on the human environment, the obvious question arises as to whether lead in street dust varies with traffic density. It appears that in non-

urban environments, street dust ranges from 80 to 130 µg/g, whereas urban street dusts range from 1,000 to 20,000 µg/g. For the purpose of estimating potential human exposure, an average value of 90 µg/g in street dust is assumed for baseline exposure and 1500 µg/g in the discussions of urban environments.

Household dust is also a normal component of the home environment. It accumulates on all exposed surfaces, especially furniture, rugs, and windowsills. In some households of workers exposed occupationally to lead dusts, the worker may carry dust home in amounts too small for efficient removal but containing lead concentrations much higher than normal baseline values.

Most of the dust values for nonurban household environments fall in the range of 50 to 500 µg/g. A value of 300 µg/g is assumed. The only natural lead in dust would be some fraction of that derived from soil lead. A value of 10 µg/g seems reasonable, since some of the soil lead is of atmospheric origin. Children ingest about 5 times as much dust as adults, most of the excess being street dusts from sidewalks and playgrounds. Exposure to occupational lead by children would be through clothing brought home by parents.

The values derived or assumed in the preceeding sections are summarized on Table 1-8. These values represent only consumption, not absorption of lead by the human body.

1.7.6 Additional Exposures

There are many conditions, even in nonurban environments, where an individual may increase his lead exposure by choice, habit, or unavoidable circumstance. These conditions are discussed as separate exposures to be added as appropriate to the baseline of human exposure described above. Most of these additive effects clearly derive from air or dust, few from water or food. Ambient air lead concentrations are typically higher in an urban than a rural environment. This factor alone can contribute significantly to the potential lead exposure of Americans, through increases in inhaled air and consumed dust. Produce from urban gardens may also increase the daily consumption of lead. Some environments may not be related only to urban living, such as houses with interior lead paint or lead plumbing, residences near smelters or refineries, or family gardens grown on high-lead soils. Occupational exposures may also be in an urban or rural setting. These exposures, whether primarily in the occupational environment or secondarily in the home of the worker, would be in addition to other exposures in an urban location or from the special cases of lead-based paint or plumbing.

Urban atmospheres. The fact that urban atmospheres have more airborne lead than nonurban contributes not only to lead consumed by inhalation but also to increased amounts of lead in dust. Typical urban atmospheres contain 0.5-1.0 µg Pb/m^3. Other variable are the amount of indoor filtered air breathed by urban residents, the amount of time spent indoors, and the amount of time spent on freeways. Dusts vary from 500 to 3000 µg/g in urban environments.

TABLE 1-8. SUMMARY OF BASELINE HUMAN EXPOSURES TO LEAD
Units are in mg/day

Source	Total Lead Consumed	Soil		Direct Atmospheric Lead*	Lead from Solder or Other Metals	Lead of Undetermined Origin
		Natural Lead Consumed	Indirect Atmospheric Lead*			
Child-2 yr old						
Inhaled Air	0.5	0.001	-	0.5	-	-
Food	28.7	0.9	0.9	10.9	10.3	17.6
Water & beverages	11.5	0.01	2.1	1.2	7.8	-
Dust	21.0	0.6	-	19.0	-	1.4
Total	61.4	1.5	3.0	31.6	18.1	19.0
Percent	100%	2.4%	4.9%	51.5%	29.5%	22.6%
Adult female						
Inhaled air	1.0	0.002	-	1.0	-	-
Food	33.2	1.0	1.0	12.6	11.9	21.6
Water & beverages	17.9	0.01	3.4	2.0	12.5	-
Dust	4.5	0.2	-	2.9	-	1.4
Total	56.6	1.2	4.4	18.5	24.4	23.0
Percent	100%	2.1%	7.8%	32.7%	43.1%	26.8%
Adult male						
Inhaled air	1.0	0.002	-	1.0	-	-
Food	45.7	1.4	1.4	17.4	16.4	31.5
Water & beverages	25.1	0.1	4.7	2.8	17.5	-
Dust	4.5	0.2	-	2.9	-	1.4
Total	76.3	1.7	6.1	24.1	33.9	32.9
Percent	100%	2.2%	8.0%	31.6%	44.4%	27.1%

*Indirect atmospheric lead has been previously incorporated into soil, and will probably remain in the soil for decades or longer. Direct atmospheric lead has been deposited on the surfaces of vegetation and living areas or incorporated during food processing shortly before human consumption.

Houses with interior lead paint. In 1974, the Consumer Product Safety Commission collected household paint samples and analyzed them for lead content (National Academy of Sciences, National Research Council, 1976).

Flaking paint can cause elevated lead concentrations in nearby soil. For example, Hardy et al. (1971) measured soil lead levels of 2000 μg/g next to a barn in rural Massachusetts. A steady decrease in lead level with increasing distance from the barn was shown, reaching 60 μg/g at fifty feet from the barn. Ter Haar and Arnow (1974) reported elevated soil lead levels in Detroit near eighteen old wood frame houses painted with lead-based paint. The average soil lead level within two feet of a house was just over 2000 μg/g; the average concentration at ten feet was slightly more than 400 μg/g. The same author reported smaller soil lead elevations in the vicinity of eighteen brick veneer houses in Detroit. Soil lead levels near painted barns located in rural areas were similar to urban soil lead concentrations near painted houses, suggesting the importance of leaded paint at both urban and rural locations. The baseline lead concentration for household dust of 300 μg/g was increased to 2000 μg/g for houses with interior lead based paints. The additional 1700 μg/g would add 85 μg Pb/day to the potential exposure of a child. This increase would occur in an urban or nonurban environment and would be in addition to the urban residential increase if the lead-based painted house were in an urban environment.

Family gardens. Several studies have shown potentially higher lead exposure through the consumption of home-grown produce from family gardens grown on high lead soils or near sources of atmospheric lead. In family gardens, lead may reach the edible portions of vegetables by deposition of atmospheric lead directly onto aboveground plant parts or onto soil, or by the flaking of lead-containing paint chips from houses. Air concentrations and particle size distributions are the important determinants of deposition to soil or vegetation surfaces. Even at relatively high air concentrations (1.5 $\mu g/m^3$) and deposition velocity (0.5 cm/sec), it is unlikely that surface deposition alone can account for more than 2-5 μg/g lead on the surface of lettuce during a 21-day growing period. It appears that a significant fraction of the lead in both leafy and root vegetables derives from the soil.

Houses with lead plumbing. The Glasgow Duplicate Diet Study (United Kingdom Directorate on Environmental Pollution, 1982) reports that children approximately 13 weeks old living in lead-plumbed houses consume 6-480 μg Pb/day. Water lead levels in the 131 homes studied ranged from less than 50 to over 500 μg/l. Those children and mothers living in the homes containing high water lead levels generally had greater total lead consumption and higher blood lead levels, according to the study. Breast-fed infants were exposed to much less lead than bottle-fed infants. The results of the study suggest that infants living in lead-plumbed homes may have exposure to considerable amounts of lead. This conclusion was also demonstrated by Sherlock et al. (1982) in a duplicate diet study in Ayr, Scotland.

Residences near smelters and refineries. Air concentrations within 2 km of lead smelters and refineries average 5-15 $\mu g/m^3$. Between inhaled air and dust, a child in this circumstance would be exposed to 1300 µg Pb/day above background levels. Exposures to adults would be much less, since they consume only 20 percent of the dusts children consume.

Occupational exposures. The highest and most prolonged exposures to lead are found among workers in the lead smelting, refining, and manufacturing industries (World Health Organization, 1977). In all work areas, the major route of lead exposure is by inhalation and ingestion of lead-bearing dusts and fumes. Airborne dusts settle out of the air onto food, water, the workers' clothing, and other objects, and may be subsequently transferred to the mouth. Therefore, good housekeeping and good ventilation have a major impact on exposure. Even tiny amounts (10 mg) of 100,000 µg/g dust can account for 1,000 µg/day exposure.

The greatest potential for high-level occupational exposure exists in the process of lead smelting and refining. The most hazardous operations are those in which molten lead and lead alloys are brought to high temperatures, resulting in the vaporization of lead, because condensed lead vapor or fume has, to a substantial degree, a small (respirable) particle size range.

When metals that contain lead or are protected with a lead-containing coating are heated in the process of welding or cutting, copious quantities of lead in the respirable size range may be emitted. Under conditions of poor ventilation, electric arc welding of zinc silicate-coated steel (containing 29 mg Pb/in^2 of coating) produces breathing-zone concentrations of lead reaching 15,000 $\mu g/m^3$, far in excess of 450 $\mu g/m^3$, the current occupational short-term exposure limit in the United States. In a study of salvage workers using oxy-acetylene cutting torches on lead-painted structural steel under conditions of good ventilation, breathing-zone concentrations of lead averaged 1200 $\mu g/m^3$ and ranged as high as 2400 $\mu g/m^3$.

At all stages in battery manufacture except for final assembly and finishing, workers are exposed to high air lead concentrations, particularly lead oxide dust. Excessive concentrations, as great as 5400 $\mu g/m^3$, have been quoted by the World Health Organization (1977). The hazard in plate casting, which is a molten-metal operation, is from the spillage of molten waste products, resulting in dusty floors.

Workers involved in the manufacture of both tetraethyl lead and tetramethyl lead, two alkyl lead compounds, are exposed to both inorganic and alkyl lead. The major potential hazard in the manufacture of tetraethyl lead and tetramethyl lead is from skin absorption, but this is guarded against by the use of protective clothing.

In both the rubber products industry and the plastics industry there are potentially high exposures to lead. The potential hazard of the use of lead stearate as a stabilizer in the manufacture of polyvinyl chloride was noted in the 1971 United Kingdom Department of Employment, Chief Inspector of Factories (1972). The source of this problem is the dust that is

generated when the lead stearate is milled and mixed with the polyvinyl chloride and the plasticizer. An encapsulated stabilizer that greatly reduces the occupational hazard is reported by Fischbein et al. (1982). Sakurai et al. (1974), in a study of bioindicators of lead exposure, found ambient air concentrations averaging 58 $\mu g/m^3$ in the lead-covering department of a rubber hose manufacturing plant.

The manufacture of cans with leaded seams may expose workers to elevated environmental lead levels. Bishop (1980) reports airborne lead concentrations of 25 to 800 $\mu g/m^3$ in several can manufacturing plants in the United Kingdom. Between 23 percent and 54 percent of the airborne lead was associated with respirable particles. Firing ranges may be characterized by high airborne lead concentrations, hence instructors who spend considerable amounts of time in such areas may be exposed to lead. Anderson et al. (1977) discuss plumbism in a 17-year-old male employee of a New York City firing range, where airborne lead concentrations as great as 1000 $\mu g/m^3$ were measured during sweeping operations. Removal of leaded paint from walls and other surfaces in old houses may pose a health hazard. Feldman (1978) reports an airborne lead concentration of 510 $\mu g/m^3$, after 22 minutes of sanding an outdoor post coated with paint containing 2.5 mg Pb/cm^2. After only five minutes of sanding an indoor window sill containing 0.8-0.9 mg Pb/cm^2, the air contained 550 $\mu g/m^3$. Garage mechanics may be exposed to excessive lead concentrations. Clausen and Rastogi (1977) report airborne lead levels of 0.2-35.5 $\mu g/m^3$ in ten garages in Denmark; the greatest concentration was measured in a paint workshop. Used motor oils were found to contain 1500-3500 μg Pb/g, while one brand of gear oil, unused, contained 9280 μg Pb/g. The authors state that absorption through damaged skin could be an important exposure pathway. Other occupations involving risk of lead exposure include stained glass manufacturing and repair, arts and crafts, and soldering and splicing.

Secondary occupational exposure. The amount of lead contained in pieces of cloth 1 in^2 cut from bottoms of trousers worn by lead workers ranged from 700 to 19,000 μg, with a median of 2,640 μg. In all cases, the trousers were worn under coveralls. Dust samples from 25 households of smelter workers ranged from 120 to 26,000 $\mu g/g$, with a median of 2,400 $\mu g/g$.

Special habits or activities. The quantity of food consumed per body weight varies greatly with age and somewhat with sex. A two-year-old child weighing 14 kg eats and drinks 1.5 kg food and water per day. This is 110 g/kg, or 3 times the consumption of an 80 kg adult male, who eats 39 g/kg.

Children place their mouths on dust collecting surfaces and lick non-food items with their tongues. This fingersucking and mouthing activity are natural forms of behavior for young children which expose them to some of the highest concentrations of lead in their environment. A single gram of dust may contain ten times more lead than the total diet of the child.

Lead is also present in tobacco. The World Health Association (1977) estimates a lead content of 2.5-12.2 μg per cigarette; roughly two to six percent of this lead may be inhaled by the smoker. The National Academy of Sciences (1980) has used these data to conclude that a typical urban resident who smokes 30 cigarettes per day may inhale roughly equal amounts of lead from smoking and from breathing urban air. The average adult consumption of table wine in the U.S. is about 12 g. Even at 0.1 μg/g, which is ten times higher than drinking water, wine does not appear to represent a significant potential exposure. At one liter/day, however, lead consumption would be greater than the total baseline consumption. McDonald (1981) points out that older wines with lead foil caps may represent a hazard, especially if they have been damaged or corroded. Wai et al. (1979) found the lead content of wine rose from 200 to 1200 μg/liter when the wine was allowed to pass over the thin ring of residue left by the corroded lead foil cap. Newer wines (1971 and later) use other means of sealing.

Pica is the compulsive, habitual consumption of non-food items. In the case of paint chips and soil, this habit can present a significant lead exposure to the afflicted person. There are very little data on the amounts of paint or soil eaten by children with varying degrees of pica. Exposure can only be expressed on a unit basis. Billick and Gray (1978) report lead concentrations of 1000-5000 $\mu g/cm^2$ in lead-based paint pigments. A single chip of paint can represent greater exposure than any other source of lead. A gram of urban soil may have 150-2000 μg lead.

Beyond the baseline level of human exposure, additional amounts of lead consumption are largely a matter of individual choice or circumstance. Most of these additional exposures arise directly or indirectly from atmospheric lead, and in one or more ways probably affect 90 percent of the American population. In some cases, the additive exposure can be fully quantified and the amount of lead consumed can be added to the baseline consumption. These may be continuous (urban residence), or seasonal (family gardening) exposures. Some factors can be quantified on a unit basis because of wide ranges in exposure duration or concentration. For example, factors affecting occupational exposure are air lead concentrations (10-4000 $\mu g/m^3$), use and efficiency of respirators, length of time of exposure, dust control techniques, and worker training in occupational hygiene.

Ambient airborne lead concentrations showed no marked trend from 1965 to 1977. Over the past five years, however, distinct decreases occurred. Mean urban air concentration has dropped from 0.91 $\mu g/m^3$ 1977 to 0.32 $\mu g/m^3$ in 1980. These decreases reflect the smaller lead emissions from mobile sources in recent years. Airborne size distribution data indicate that most of the airborne lead mass is found in submicron particles. Atmospheric lead is deposited on vegetation and soil surfaces, entering the human food chain through contamination of grains and leafy vegetables, of pasture lands, and of soil moisture taken up by all crops. Lead contamination of drinking water supplies appears to originate mostly from within the distribution system.

Most people receive the largest portion of their lead intake through foods. Unprocessed foods such as fresh fruits and vegetables receive lead by atmospheric deposition as well as uptake from soil; crops grown near heavily traveled roads generally have greater lead levels than those grown at greater distances from traffic. For many crops the edible internal portions of the plant (e.g., kernels of corn and wheat) have considerably less lead than the outer, more exposed parts such as stems, leaves, and husks. Atmospheric lead accounts for about 30 percent of the total adult lead exposure, and 50 percent of the exposure for children. Processed foods have greater lead concentrations than unprocessed foods, due to lead inadvertently added during processing. Foods packaged in soldered cans have much greater lead levels than foods packaged in other types of containers. About 45 percent of the baseline adult exposure to lead results from the use of solder lead in packaging food and distributing drinking water.

Significant amounts of lead in drinking water can result from contamination at the water source and from the use of lead solder in the water distribution system. Atmospheric deposition has been shown to increase lead in rivers, reservoirs, and other sources of drinking water; in some areas, however, lead pipes pose a more serious problem. Soft, acidic water in homes with lead plumbing may have excessive lead concentrations. Besides direct consumption of the water, exposure may occur when vegetables and other foods are cooked in water containing lead.

All of the categories of potential lead exposure discussed above may influence or be influenced by dust and soil. For example, lead in street dust is derived primarily from vehicular emissions, while leaded house dust may originate from nearby stationary or mobile sources. Food and water may include lead adsorbed from soil as well as deposited atmospheric material. Flaking leadbased paint has been shown to increase soil lead levels. Natural concentrations of lead in soil average approximately 15 µg/g; this natural lead, in addition to anthropogenic lead emissions, influences human exposure.

Americans living in rural areas away from sources of atmospheric lead consume 50 to 75 µg Pb/day from all sources. Circumstances which can increase this exposure are: urban residence (25 to 100 µg/day), family garden on high lead soil (800 to 2000 µg/day), houses with interior lead-based paint (20 to 85 µg/day), and residence near a smelter (400 to 1300 µg/day). Occupational settings, smoking and wine consumption also can increase consumption of lead according to the degree of exposure.

A number of manmade materials are known to contain lead, the most important being paint and plastics. Lead-based paints, although no longer used, are a major problem in older homes. Small children who ingest paint flakes can receive excessive lead exposure. Incineration of plastics may emit large amounts of lead into the atmosphere. Because of the increasing use of

plastics, this source is likely to become more important. Other manmade materials containing lead include colored dyes, cosmetic products, candle wicks, and products made of pewter and silver.

The greatest occupational exposures are found in the lead smelting and refining industries. Excessive airborne lead concentrations and dust lead levels are occasionally found in primary and secondary smelters; smaller exposures are associated with mining and processing of the lead ores. Welding and cutting of metal surfaces coated with lead-based paint may also result in excessive exposure. Other occupations with potentially high exposures to lead include the manufacture of lead storage batteries, printing equipment, alkyl lead, rubber products, plastics, and cans; individuals removing lead paint from walls and those who work in indoor firing ranges may also be exposed to lead.

Environmental contamination by lead should be measured in terms of the total amount of lead emitted to the biosphere. American industry contributes several hundred thousand tons of lead to the environment each year: 35,000 tons from petroleum additives, 50,000 tons from ammunition, 45,000 tons in glass and ceramic products, 16,000 tons in paint pigments, 8,000 tons in food can solder, and untold thousands of tons of captured wastes during smelting, refining, and coal combustion. These are uses of lead which are generally not recoverable, thus they represent a permanent contamination of the human or natural environment. Although much of this lead is confined to municipal and industrial waste dumps, a large amount is emitted to the atmosphere, waterways, and soil, to become a part of the biosphere.

Potential human exposure can be expressed as the concentrations of lead in those environmental components (air, dust, food, and water) that interface with man. It appears that, with the exception of extraordinary cases of exposure, about 100 mg of lead are consumed daily by each American. This amounts to only 8 tons, or less than 0.01 percent of the total environmental contamination.

1.8 EFFECTS OF LEAD ON ECOSYSTEMS

The principle sources of lead entering an ecosystem are: the atmosphere (from automotive emissions), paint chips, spent ammunition, the application of fertilizers and pesticides, and the careless disposal of lead-acid batteries or other industrial products. Atmospheric lead is deposited on the surfaces of vegetation as well as on ground and water surfaces. In terrestrial ecosystems, this lead is transferred to the upper layers of the soil surface, where it may be retained for a period of several years. The movement of lead within ecosystems is influenced by the chemical and physical properties of lead and by the biogeochemical properties of the ecosystem. Lead is non-degradable, but in the appropriate chemical environment, may undergo transformations which affect its solubility (e.g., formation of lead sulfate

in soils), its bioavailability (e.g., chelation with humic substances), or its toxicity (e.g., chemical methylation). Although the situation is extremely complex, it is reasonable to state that most plants cannot survive in soil containing 10,000 μg lead/g dry weight if the pH is below 4.5 and the organic content is below 5 percent.

There is wide variation in the mass transfer of lead from the atmosphere to terrestrial ecosystems. Smith and Siccama (1981) report 270 g/ha·yr in the Hubbard Brook forest of New Hampshire, Lindberg and Harriss (1981) found 50 g/ha·yr in the Walker Branch watershed of Tennessee; and Elias et al. (1976) found 15 g/ha·yr in a remote subalpine ecosystem of California. Jackson and Watson (1977) found 1,000,000 g/ha·yr near a smelter in southeastern Missouri. Getz et al. (1979) estimated 240 g/ha·yr by wet precipitation alone in a rural ecosystem largely cultivated, and 770 g/ha·yr in an urban ecosystem.

One factor causing great variation is remoteness from source, which translates to lower air concentrations, smaller particles, and greater dependence on wind as a mechanism of deposition. Another factor is type of vegetation cover. Deciduous leaves may, by the nature of their surface and orientation in the wind stream, be more suitable deposition surfaces than conifer needles.

There are three known conditions under which lead may perturb ecosystem processes (see Figured 1-12). At soil concentrations of 1000 μg/g or higher, delayed decomposition may result from the elimination of a single population of decomposer microorganisms. Secondly, at concentrations of 500-1000 μg/g, populations of plants, microorganisms, and invertebrates may shift toward lead tolerant populations of the same or different species. Finally, the normal biogeochemical process which purifies and repurifies calcium in grazing and decomposer food chains may be circumvented by the addition of lead to vegetation and animal surfaces. This third effect can be measured at all ambient atmospheric concentrations of lead.

Some additional effects may occur due to the uneven distribution of lead in ecosystems. It is known that lead accumulates in soil, especially soil with high organic content. Although no firm documentation exists, it is reasonable to assume from the known chemistry of lead in soil that: (1) other metals may be displaced from binding sites on the organic matter; (2) the chemical breakdown of inorganic soil fragments may be retarded by interference of lead with the action of fulvic acid on iron bearing crystals; and (3) lead in soil may be in equilibrium with moisture films surrounding soil particles and thus available for uptake by plants.

Two principles govern ecosystem functions: (1) energy flows through an ecosystem; and (2) nutrients cycle within an ecosystem. Energy usually enters the ecosystem in the form of sunlight and leaves as heat of respiration. Unlike energy, nutrient and non-nutrient elements are recycled by the ecosystem and transferred from reservoir to reservoir in a pattern usually

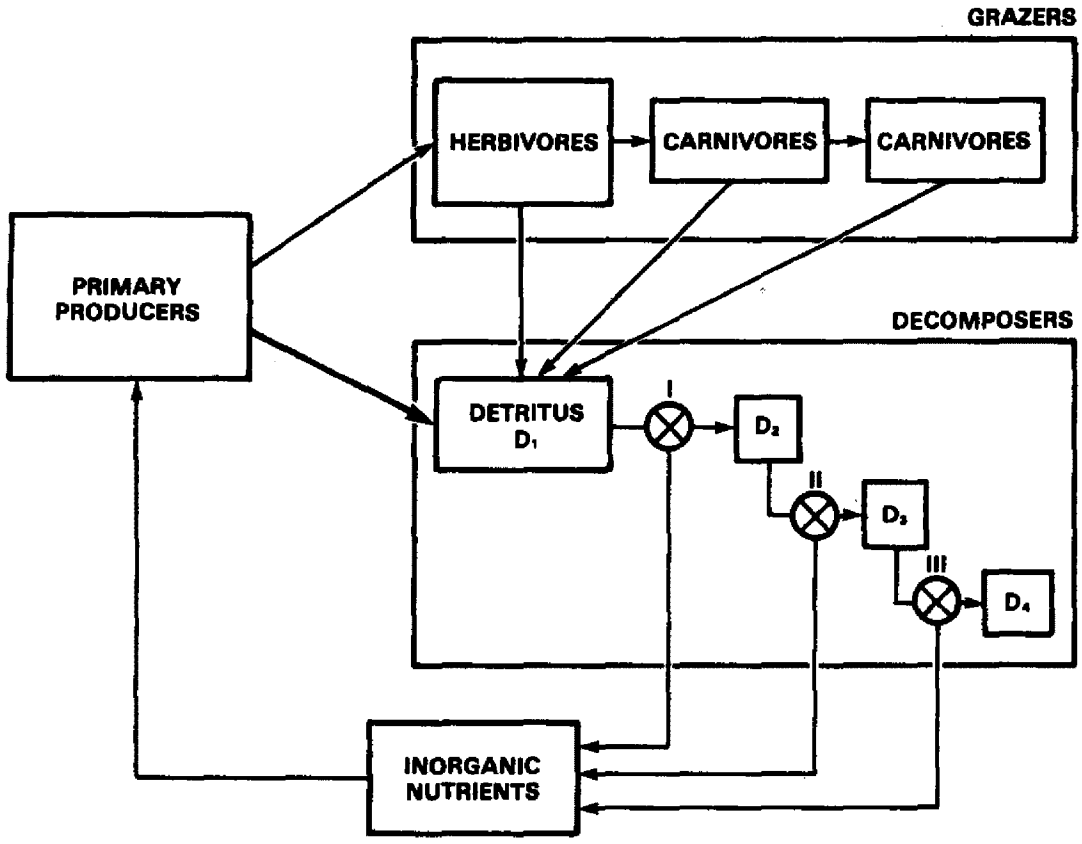

Figure 1-12. This figure depicts cycling processes within the major components of a terrestrial ecosystem, i.e. primary producers, grazers and decomposers. Nutrient and non-nutrient elements are stored in reservoirs within these components. Processes that take place within reservoirs regulate the flow of elements between reservoirs along established pathways. The rate of flow is in part a function of the concentration in the preceding reservoir. Lead accumulates in decomposer reservoirs which have a high binding capacity for this metal. It is likely that the rate of flow away from these reservoirs has increased in past decades and will continue to increase for some time until the decomposer reservoirs are in equilibrium with the entire ecosystem. Inputs to and outputs from the ecosystem as a whole are not shown.

Source: Adapted from Swift et al. (1979).

referred to as a biogeochemical cycle (Brewer, 1979, p. 139). The reservoirs correspond approximately to the food webs of energy flow. Although elements may enter (e.g., weathering of soil) or leave the ecosystem (e.g., stream runoff), the greater fraction of the available mass of the element is usually cycled within the ecosystem.

Ecosystems have boundaries. These boundaries may be as distinct as the border of a pond or as arbitrary as an imaginary circle drawn on a map. Many trace metal studies are conducted in watersheds where some of the boundaries are determined by topography. For atmospheric inputs to terrestrial ecosystems, the boundary is usually defined as the surface of vegetation, exposed rock or soil. Non-nutrient elements differ little from nutrient elements in their biogeochemical cycles. Quite often, the cycling patterns are similar to those of a major nutrient. In the case of lead, the reservoirs and pathways are very similar to those of calcium.

Naturally occurring lead from the earth's crust is commonly found in soils and the atmosphere. Lead may enter an ecosystem by weathering of parent rock or by deposition of atmospheric particles. This lead becomes a part of the nutrient medium of plants and the diet of animals. All ecosystems receive lead from the atmosphere.

In prehistoric times, the contribution of lead from weathering of soil was probably about 4g Pb/ha·yr and from atmospheric deposition about 0.02 g Pb/ha·yr. Weathering rates are presumed to have remained the same, but atmospheric inputs are believed to have increased to 180 g/ha·yr in natural and some cultivated ecosystems, and 3000 g/ha·yr in urban ecosystems and along roadways. In every terrestrial ecosystem of the Northern Hemisphere, atmospheric lead deposition now exceeds weathering by a factor of at least 10, sometimes by as much as 1000.

Many of the effects of lead on plants, microorganisms, and ecosystems arise from the fact that lead from atmospheric and weathering inputs is retained by soil. Geochemical studies show that less than 3 percent of the inputs to a watershed leave by stream runoff. Lead in natural soils now accumulates on the surface at an annual rate of 5-10 percent of the natural lead. One effect of cultivation is that atmospheric lead is mixed to a greater depth than the 0-3 cm of natural soils.

Most of the effects on grazing vertebrates stem from the deposition of atmospheric particles on vegetation surfaces. Atmospheric deposition may occur by either of two mechanisms. Wet deposition (precipitation scavenging through rainout or washout) generally transfers lead directly to the soil. Dry deposition transfers particles to all exposed surfaces. Large particles (>4 μm) are transferred by gravitational mechanisms, small particles (<0.5 μm) are also deposited by wind-related mechanisms.

If the air concentration is known, ecosystem inputs from the atmosphere can be predicted over time and under normal conditions. These inputs and those from the weathering of soil

determine the concentration of lead in the nutrient media of plants, animals, and microorganisms. It follows that the concentration of lead in the nutrient medium determines the concentration of lead in the organism and this in turn determines the effects of lead on the organism. The fundamental nutrient medium of a terrestrial ecosystem is the soil moisture film which surrounds organic and inorganic soil particles. This film of water is in equilibrium with other soil components and provides dissolved inorganic nutrients to plants.

Studies have shown the lead content of leafy vegetation to be 90 percent anthropogenic, even in remote areas (Crump and Barlow, 1980; Elias et al., 1976, 1978). The natural lead content of nuts and fruits may be somewhat higher than leafy vegetation, based on internal lead concentrations of modern samples (Elias et al. 1982).

Because lead in soil is the source of most effects on plants, microorganisms, and ecosystems, it is important to understand the processes that control the accumulation of lead in soil. Major components of soil are: (1) fragments of inorganic parent rock material; (2) secondary inorganic minerals; (3) organic constituents, primarily humic substances, which are residues of decomposition or products of decomposer organisms; (4) Fe-Mn oxide films, which coat the surfaces of all soil particles and have a high binding capacity for metals; (5) soil microorganisms, most commonly bacteria and fungi, although protozoa and soil algae may also be found; and (6) soil moisture, the thin film of water surrounding soil particles which is the nutrient medium of plants.

The concentration of lead ranges from 5 to 30 μg/g in the top 5 cm of most soils not adjacent to sources of industrial lead, although 5 percent of the soils contain as much as 800 μg/g. Aside from surface deposition of atmospheric particles, plants in North America average about 0.5-1 μg/g dw (Peterson, 1978) and animals roughly 2 μg/g (Forbes and Sanderson, 1978). Thus, soils contain the greater part of total ecosystem lead. In soils, lead in parent rock fragments is tightly bound within the crystalline structures of the inorganic soil minerals. It is released to the ecosystem only by surface contact with soil moisture films.

Hutchinson (1980) has reviewed the effects of acid precipitation on the ability of soils to retain cations. Excess calcium and other metals are leached from the A horizon of soils by rain with a pH more acidic than 4.5. Most soils in the eastern United States are normally acidic (pH 3.5-5.2) and the leaching process is a part of the complex equilibrium maintained in the soil system. By increasing the leaching rate, acid rain can reduce the availability of nutrient metals to organisms dependent on the top layer of soil. It appears that acidification of soil may increase the rate of removal of lead from the soil, but not before several major nutrients are removed first. The effect of acid rain on the retention of lead by soil moisture is not known.

Atmospheric lead may enter aquatic ecosystems by wet or dry deposition or by the erosional transport of soil particles. In waters not polluted by industrial, agricultural, or

municipal effluents, the lead concentration is usually less than 1 µg/l. Of this amount, approximately 0.02 µg/l is natural lead and the rest is anthropogenic lead, probably of atmospheric origin (Patterson, 1980). Surface waters mixed with urban effluents may frequently reach lead concentrations of 50 µg/l, and occasionally higher. In still water, lead is removed from the water column by the settling of lead-containing particulate matter, by the formation of insoluble complexes, or by the adsorption of lead onto suspended organic particles. The rate of sedimentation is determined by temperature, pH, oxidation-reduction potential, ionic competition, the chemical form of lead in water, and certain biological activities (Jenne and Luoma, 1977). McNurney et al. (1977) found 14 µg Pb/g in stream sediments draining cultivated areas and 400 µg/g in sediments associated with urban ecosystems.

1.8.1 Effects on Plants

Some physiological and biochemical effects of lead on vascular plants have been detected under laboratory conditions at concentrations higher than normally found in the environment. The commonly reported effects are the inhibition of photosynthesis, respiration or cell elongation, all of which reduce the growth of the plant (Koeppe, 1981). Lead may also induce premature senescence, which may affect the long-term survival of the plant or the ecological success of the plant population. Most of the lead in or on a plant occurs on the surfaces of leaves and the trunk or stem. The surface concentration of lead in trees, shrubs, and grasses exceeds the internal concentration by a factor of at least five (Elias et al, 1978). There is little or no evidence of lead uptake through leaves or bark. Foliar uptake, if it does occur, cannot account for more than 1 percent of the uptake by roots, and passage of lead through bark tissue has not been detected (Arvik and Zimdahl, 1974; reviewed by Koeppe, 1981; Zimdahl, 1976). The major effect of surface lead at ambient concentrations seems to be on subsequent components of the grazing food chain and on the decomposer food chain following litterfall (Elias et al., 1982).

Uptake by roots is the only major pathway for lead into plants. The amount of lead that enters plants by this route is determined by the availability of lead in soil, with apparent variations according to plant species. Soil cation exchange capacity, a major factor, is determined by the relative size of the clay and organic fractions, soil pH, and the amount of Fe-Mn oxide films present (Nriagu, 1978). Of these, organic humus and high soil pH are the dominant factors in immobilizing lead. Under natural conditions, most of the total lead in soil would be tightly bound within the crystalline structure of inorganic soil fragments, unavailable to soil moisture. Available lead, bound on clays, organic colloids, and Fe-Mn films, would be controlled by the slow release of bound lead from inorganic rock sources. Because lead is strongly immobilized by humic substances, only a small fraction (perhaps 0.01 - percent in soils with 20 percent organic matter, pH 5.5) is released to soil moisture.

Two defensive mechanims appear to exist in the roots of plants for removing lead from the stream of nutrients flowing to the above-ground portions of plants. Lead may be deposited with cell wall material exterior to the individual root cells, or may be sequestered in organelles within the root cells. Any lead not captured by these mechanisms would likely move with nutrient metals cell-to-cell through the symplast and into the vascular system. Uptake of lead by plants may be enhanced by symbiotic associations with mycorrhizal fungi. The three primary factors that control the uptake of nutrients by plants are the surface area of the roots, the ability of the root to absorb particular ions, and the transfer of ions through the soil. The symbiotic relationship between mycorrhizal fungi and the roots of higher plants can increase the uptake of nutrients by enhancing all three of these factors.

The translocation of lead to aboveground portions of the plant is not clearly understood. Lead may follow the same pathway and be subject to the same controls as a nutrient metal such as calcium. There may be several mechanisms that prevent the translocation of lead to other plant parts. The primary mechanisms may be storage in cell organelles or adsorption on cell walls. Some lead passes into the vascular tissue, along with water and dissolved nutrients, and is carried to physiologically active tissue of the plant. Evidence that lead in contaminated soils can enter the vascular system of plants and be transported to aboveground parts may be found in the analysis of tree rings. These chronological records confirm that lead can be translocated in proportion to the concentrations of lead in soil.

Because most of the physiologically active tissue of plants is involved in growth, maintenance, and photosynthesis, it is expected that lead might interfere with one or more of these processes. Indeed, such interferences have been observed in laboratory experiments at lead concentrations greater than those normally found in the field, except near smelters or mines (Koeppe, 1981). Inhibition of photosynthesis by lead may be by direct interference with the light reaction or the indirect interference with carbohydrate synthesis. Miles et al. (1972) demonstrated substantial inhibition of photosystem II near the site of water splitting, a biochemical process believed to require manganese. Devi Prasad and Devi Prasad (1982) found 10 percent inhibition of pigment production in three species of green algae at 1 µg/g, increasing to 50 percent inhibition at 3 µg/g. Bazzaz et al. (1974, 1975) observed reduced net photosynthesis which may have been caused indirectly by inhibition of carbohydrate synthesis.

The stunting of plant growth may be by the inhibition of the growth hormone IAA (indole-3-ylacetic acid). Lane et al. (1978) found a 25 percent reduction in elongation at 10 µg/g lead as lead nitrate in the nutrient medium of wheat coleoptiles. Lead may also interfere with plant growth by reducing respiration or inhibiting cell division. Miller and Koeppe (1971) and Miller et al. (1975) showed succinate oxidation inhibition in isolated mitochondria as well as stimulation of exogenous NADH oxidation with related mitochondrial swelling.

Hassett et al. (1976), Koeppe (1977), and Malone et al. (1978) described significant inhibition of lateral root initiation in corn. The interaction of lead with calcium has been shown by several authors, most recently by Garland and Wilkins (1981), who demonstrated that barley seedlings (Hordeum vulgare), which were growth inhibited at 2 µg Pb/g sol. with no added calcium, grew at about half the control rate with 17 µg Ca/g sol. This relation persisted up to 25 µg Pb/g sol. and 500 µg Ca/g sol.

These studies of the physiological effects of lead on plants all show some effect at concentrations from 2 to 10 µg/g in the nutrient medium of hydroponically-grown agricultural plants. It is certain that no effects would have been observed at these concentrations had the lead solutions been added to normal soil, where the lead would have been bound by humic substances. There is no firm relationship between soil lead and soil moisture lead, because each soil type has a unique capacity to retain lead and to release that lead to the soil moisture film surrounding the soil particle. Once in soil moisture, lead seems to pass freely to the plant root according to the capacity of the plant root to absorb water and dissolved substances.

It seems reasonable that there may be a direct correlation between lead in hydroponic media and lead in soil moisture. Hydroponic media typically have an excess of essential nutrients, including calcium and phosphorus, so that movement of lead from hydroponic media to plant root would be equal to or slower than movement from soil moisture to plant root.

Even under the best of conditions where soil has the highest capacity to retain lead, most plants would experience reduced growth rate (inhibition of photosynthesis, respiration, or cell elongation) in soils containing 10,000 µg Pb/g or greater. Concentrations approaching this value typically occur around smelters and near major highways. These conclusions pertain to soil with the ideal composition and pH to retain the maximum amount of lead. Acid soils or soils lacking organic matter would inhibit plants at much lower lead concentrations.

The rate at which atmospheric lead accumulates in soil varies from 1.1 $mg/m^2 \cdot yr$ average global deposition to 3000 $mg/m^2 \cdot yr$ near a smelter. Assuming an average density of 1.5 g/cm^3, undisturbed soil to a depth of 2 cm (20,000 cm^3/m^2) would incur an increase in lead concentration at a rate of 0.04 to 100 µg/g soil·yr. This means remote or rural area soils may never reach the 10,000 µg/g threshold but that undisturbed soils closer to major sources may be within range in the next 50 years.

Some plant species have developed populations tolerant to high lead soils. Using populations taken from mine waste and uncontaminated control areas, some authors have quantified the degree of tolerance of Agrostis tenuis (Karataglis, 1982) and Festuca rubra (Wong, 1982) under controlled laboratory conditions. Root elongation was used as the index of tolerance. At 36 µg Pb/g nutrient solution, all populations of A. tenuis were completely inhibited. At 12 µg Pb/g, the control populations from low lead soils were completely inhibited, but the

populations from mine soils achieved 30 percent of their normal growth (growth at no lead in nutrient solution). At 6 µg/g, the control populations achieved 10 percent of their normal growth, tolerant populations achieved 42 percent. There were no measurements below 6 µg/g. These studies support the conclusion that inhibition of plant growth begins at a lead concentration of less than 1 µg/g soil moisture and becomes completely inhibitory at a level between 3 and 10 µg/g. Plant populations that are genetically adapted to high lead soils may achieve 50 percent of their normal root growth at lead concentrations above 3 µg/g.

When soil conditions allow lead concentrations in soil moisture to exceed 2-10 µg/g, most plants experience reduced growth due to the inhibition of one or more physiological processes. Excess calcium or phosphorus may reverse the effect. Plants that absorb nutrients from deeper soil layers may receive less lead. Acid rain is not likely to release more lead until after major nutrients have been depleted from the soil. A few species of plants have the genetic capability to adapt to high lead soils.

Tyler (1972) explained three ways in which lead might interfere with the normal decomposition processes in a terrestrial ecosystem. Lead may be toxic to specific groups of decomposers, it may deactivate enzymes excreted by decomposers to break down organic matter, or it may bind with the organic matter to render it resistant to the action of decomposers. Because lead in litter may selectively inhibit decomposition by soil bacteria at 2000-5000 µg/g, forest floor nutrient cycling processes may be seriously disturbed near lead smelters. This is especially important because approximately 70 percent of plant biomass enters the decomposer food chain. If decomposition of the biomass is inhibited, then much of the energy and nutrients remain unavailable to subsequent components of the food chain. There is also the possibility that the ability of soil to retain lead would be reduced, as humic substances are byproducts of bacterial decomposition. Because they are interdependent, the absence of one decomposer group in the decomposition food chain seriously affects the success of subsequent groups, as well as the rate at which plant tissue decomposes. Each group may be affected in a different way and at different lead concentrations. Lead concentrations toxic to decomposer microbes may be as low as 1 to 5 µg/g or as high as 5000 µg/g. Under conditions of mild contamination, the loss of one sensitive bacterial population may result in its replacement by a more lead-tolerant strain. Delayed decomposition has been reported near smelters, mine waste dumps, and roadsides. This delay is generally in the breakdown of litter from the first stage (O_1) to the second (O_2), with intact plant leaves and twigs accumulating at the soil surface. The substrate concentrations at which lead inhibits decomposition appear to be very low.

The conversion of ammonia to nitrate in soil is a two-step process mediated by two genera of bacteria, Nitrosomonas and Nitrobacter. Nitrate is required by all plants, although some

maintain a symbiotic relationship with nitrogen-fixing bacteria as an alternate source of nitrogen. Those which do not would be affected by a loss of free-living nitrifying bacteria, and it is known that many trace metals inhibit this nitrifying process. Lead is the least of these, inhibiting nitrification 14 percent at concentrations of 1000 µg/g soil. Even a 14 percent inhibition of nitrification can reduce the potential success of a plant population, as nitrate is usually the limiting nutrient in terrestrial ecosystems.

It appears that microorganisms are more sensitive than plants to soil lead pollution and that changes in the composition of bacterial populations may be an early indication of lead effects. Delayed decomposition may occur at 750 µg Pb/g soil and nitrification inhibition at 1000 µg/g.

1.8.2 Effects on Animals

Forbes and Sanderson (1978) have reviewed reports of lead toxicity in domestic and wild animals. Lethal toxicity can usually be traced to consumption of lead battery casings, lead-based paints, oil wastes, putty, linoleum, pesticides, lead shot, or forage near smelters. Awareness of the routes of uptake is important in interpreting the exposure and accumulation in vertebrates. Inhalation rarely accounts for more than 10 to 15 percent of the daily intake of lead (National Academy of Sciences, 1980). Food is the largest contributor of lead to animals. The type of food an herbivore eats determines the rate of lead ingestion. More than 90 percent of the total lead in leaves and bark may be surface deposition, but relatively little surface deposition may be found on some fruits, berries, and seeds which have short exposure times. Roots intrinsically have no surface deposition. Similarly, ingestion of lead by a carnivore depends mostly on deposition on herbivore fur and somewhat less on lead in herbivore tissue.

The type of food eaten is a major determinant of lead body burdens in small mammals. Goldsmith and Scanlon (1977) and Scanlon (1979) measured higher lead concentrations in insectivorous species than in herbivorous, confirming the earlier work of Quarles et al. (1974) which showed body burdens of granivores<herbivores<insectivores, and Jeffries and French (1972) that granivores<herbivores. Chmiel and Harrison (1981) showed highest concentrations of lead in the bones of small mammals, with kidneys and livers somewhat less. They also showed greater bone concentrations in insectivores than herbivores, both at control and contaminated sites. Clark (1979) found lead concentrations in shrews, voles, and brown bats from roadside habitats near Washington, D.C., to be higher than any previously reported. There are few studies reporting lead in vertebrate tissues from remote sites. Elias et al. (1976, 1982) reported tissue concentrations in voles, shrews, chipmunks, tree squirrels, and pine martens from the remote High Sierra. Bone concentrations were generally only 2 percent of those reported from roadside studies and 10 percent of the controls of roadside studies, indicating the controls were themselves contaminated to a large degree.

Hematological and neurological responses are the most commonly reported effects of extended lead exposures in aquatic vertebrates. Hematological effects include the disabling and destruction of mature red blood cells and the inhibition of the enzyme ALA-D required for hemoglobin synthesis. At low exposures, fish compensate by forming additional red blood cells. These red blood cells often do not reach maturity. At higher exposures, the fish become anemic. Symptoms of neurological responses are difficult to detect at low exposure, but higher exposure can induce neuromuscular distortion, anorexia, and muscle tremors. Spinal curvature eventually occurs with time or increased concentration.

Insects have lead concentrations that correspond to those found in their habitat and diet. Herbivorous invertebrates have lower concentrations than do predatory types. Among the herbivorous groups, sucking insects have lower lead concentrations than chewing insects, especially in regions near roadsides, where more lead is found on vegetation surfaces. Williamson and Evans (1972) found that gradients away from roadsides are not the same as with vertebrates, in that invertebrate lead decreases more slowly than vertebrate lead relative to decreases in soil lead. In Cepaea hortensis, a terrestrial snail, Williamson (1979) found most of the lead in the digestive gland and gonadal tissue. A continuation of the study (Williamson, 1980) showed that body weight, age, and daylength influenced the lead concentrations in soft tissues. Beeby and Eaves (1983) addressed the question of whether uptake of lead in the garden snail, Helix aspersa, is related to the nutrient requirement for calcium during shell formation and reproductive activity. They found both metals were strongly correlated with changes in dry weight and little evidence for correlation of lead with calcium independent of weight gain or loss.

Gish and Christensen (1973) found lead in whole earthworms to be correlated with soil lead, with little rejection of lead by earthworms. Consequently, animals feeding on earthworms from high lead soils might receive toxic amounts of lead in their diets, although there was no evidence of toxic effects on the earthworms. Ash and Lee (1980) cleared the digestive tracts of earthworms and still found direct correlation of lead in earthworms with soil lead; in this case, soil lead was inferred from fecal analyses. Ireland and Richards (1977) also found some localization of lead in subcellular organelles of chloragogue and intestinal tissue. In view of the fact that chloragocytes are believed to be involved with waste storage and glycogen synthesis, the authors concluded that this tissue is used to sequester lead in the manner of vertebrate livers.

Borgmann et al. (1978) found increased mortality in a freshwater snail, Lymnaea palutris, associated with stream water with a lead content as low as 19 µg/l. Full life cycles were studied to estimate population productivity. Although individual growth rates were not affected, increased mortality, especially at the egg hatching stage, effectively reduced total biomass production at the population level. Production was 50 percent at 36 µg/l and 0 percent at 48 µg Pb/l.

While it is impossible to establish a safe limit of daily lead consumption, it is reasonable to generalize that a regular diet of 2 to 8 mg Pb/kg·day body weight over an extended period of time (Botts, 1977) will cause death in most animals. Animals of the grazing food chain are affected most directly by the accumulation of aerosol particles on vegetation surfaces, and somewhat indirectly by the uptake of lead through plant roots. Many of these animals consume more than 1 mg Pb/kg·day in habitats near smelters and roadsides, but no toxic effects have been documented. Animals of the decomposer food chain are affected indirectly by lead in soil which can eliminate populations of microorganisms preceeding animals in the food chain or occupying the digestive tract of animals and aiding in the breakdown of organic matter. Invertebrates may also accumultate lead at levels toxic to their predators.

Aquatic animals are affected by lead at water concentrations lower than previously considered safe (50 µg Pb/l) for wildlife. These concentrations occur commonly, but the contribution of atmospheric lead to specific sites of high aquatic lead is not clear.

1.8.3 Effects on Microoganisms

Recent studies have shown three areas of concern where the effects of lead on ecosystems may be extremely sensitive. First, decomposition is delayed by lead, as some decomposer microorganisms and invertebrates are inhibited by soil lead. Secondly, the natural processes of calcium biopurification are circumvented by the accumulation of lead on the surfaces of vegetation and in the soil reservoir. Thirdly, some ecosystems experience subtle shifts toward lead tolerant plant populations. These problems all arise because lead in ecosystems is deposited on vegetation surfaces, accumulates in the soil reservoir, and is not removed with the surface and ground water passing out of the ecosystem.

Terrestrial ecosystems, especially forests, accumulate a tremendous amount of cellulose as woody tissue of trees. Few animals can digest cellulose and most of these require symbiotic associations with specialized bacteria. It is no surprise then, that most of this cellulose must eventually pass through the decomposer food chain. Because 80 percent or more of net primary production passes through the decomposing food chain, the energy of this litter is vital to the rest of the plant community and the inorganic nutrients are vital to plants.

The amount of lead that causes litter to be resistant to decomposition is not known. Doelman and Haanstra (1979a) demonstrated the effects of soil lead content on delayed decomposition: sandy soils lacking organic complexing compounds showed a 30 percent inhibition of decomposition at 750 µg/g, including the complete loss of major bacterial species, whereas the effect was reduced in clay soils and non-existent in peat soils. Organic matter maintains the cation exchange capacity of soils. A reduction in decomposition rate was observed by Doelman and Haanstra (1979a) even at the lowest experimental concentration of lead, leading to the conclusion that some effect might have occurred at even lower concentrations.

1.8.4 Effects on Ecosystems

When decomposition is delayed, nutrients may be limiting to plants. In tropical regions or areas with sandy soils, rapid turnover of nutrients is essential for the success of the forest community. Even in a mixed deciduous forest, a significant portion of the nutrients, especially nitrogen and sulfur, may be found in the litter reservoir (Likens et al. 1977). Annual litter inputs of calcium and nitrogen to the soil account for about 60 percent of root uptake. With delayed decomposition, plants must rely on precipitation and soil weathering for the bulk of their nutrients. Furthermore, the organic content of soil may decrease, reducing the cation exchange capacity of soil.

Biopurification is a process that regulates the relative concentrations of nutrient to non-nutrient elements in biological components of a food chain. In the absence of absolute knowledge of natural lead concentrations, biopurification can be a convenient method for estimating the degree of contamination. It is now believed that members of grazing and decomposer food chains are contaminated by factors of 30-500, i.e., that 97-99.9 percent of the lead in organisms is of anthropogenic origin. Burnett and Patterson (1980) have shown a similar pattern for a marine food chain.

It has been observed that plant communities near smelter sites are composed mostly of lead tolerant plant populations. In some cases, these populations appear to have adapted to high lead soils, since populations of the same species from low lead soils often do not thrive on high lead soils. In some situations, it is clear that soil lead concentration has become the dominant factor in determining the success of plant populations and the stability of the ecological community.

Inputs of natural lead to ecosystems, approximately 90 percent from rock weathering and 10 percent from atmospheric sources, account for slightly more than the hydrologic lead outputs in most watersheds. The difference is small and accumulation in the ecosystem is significant only over a period of several thousand years. In modern ecosystems, with atmospheric inputs exceeding weathering by factors of 10-1000, greater accumulation occurs in soils and this reservoir must be treated as lacking a steady state condition. Odum and Drifmeyer (1978) describe the role of detrital particles in retaining a wide variety of pollutant substances, and this role may be extended to include non-nutrient substances.

It appears that plant communities have a built-in mechanism for purifying their own nutrient medium. As a plant community matures through successional stages, the soil profile develops a stratified arrangement which retains a layer of organic material near the surface. This organic layer becomes a natural site for the accumulation of lead and other non-nutrient metals which might otherwise interfere with the uptake and utilization of nutrient metals. But the rate of accumulation of lead in this reservoir may eventually exceed the capacity of

the reservoir. Johnson et al. (1982a) have established a baseline of 80 stations in forests of the northeast United States. In the litter component of the forest floor, they measured an average lead concentration of 150 µg/g. Near a smelter, they measured 700 µg/g and near a highway, 440 µg/g. They presented some evidence from buried litter that predevelopment concentrations were 24 µg/g.

Lead in the detrital reservoir is determined by the continued input of atmospheric lead from the litter layer, the passage of detritus through the decomposer food chain, and the rate of leaching into soil moisture. There is strong evidence that soil has a finite capacity to retain lead. Harrison et al. (1981) observed that most of the lead in roadside soils above 200 µg/g is found on Fe-Mn oxide films or as soluble lead carbonate. Lead is removed from the detrital reservoir by the digestion of organic particles in the detrital food chain and by the release of lead to soil moisture. Both mechanisms result in a redistribution of lead among all of the reservoirs of the ecosystem at a very slow rate.

Fulvic acid plays an important role in the development of the soil profile. This organic acid has the ability to remove iron from the lattice structures of inorganic minerals, resulting in the decomposition of these minerals as a part of the weathering process. This breakdown releases nutrients for uptake by plant roots. If all binding sites on fulvic acid are occupied by lead, the role of fulvic acid in providing nutrients to plants will be circumvented. While it is reasonably certain that such a process is possible, there is no information about the soil lead concentrations that would cause such an effect.

Ecosystem inputs of lead by the atmospheric route have established new pathways and widened old ones. Insignificant amounts of lead are removed by surface runoff or ground water seepage. It is likely that the ultimate fate of atmospheric lead will be a gradual elevation in lead concentration of all reservoirs in the system, with most of the lead accumulating in the detrital reservoir.

Because there is no protection from industrial lead once it enters the atmosphere, it is important to fully understand the effects of industrial lead emissions. Of the 450,000 tons emitted annually on a global basis, 115,000 tons of lead fall on terrestrial ecosystems. Evenly distributed, this would amount to 0.1 g/ha·yr, which is much lower than the range of 15 to 1,000,000 g/ha·yr reported in ecosystem studies in the United States. Lead has permeated these ecosystems and accumulated in the soil reservoir where it will remain for decades. Within 20 meters of every major highway, up to 10,000 µg Pb have been added to each gram of surface soil since 1930 (Getz et al., 1979). Near smelters, mines, and in urban areas, as much as 130,000 µg/g have been observed in the upper 2.5 cm of soil (Jennett et al., 1977). At increasing distances up to 5 kilometers away from sources, the gradient of lead added since 1930 drops to less than 10 µg/g (Page and Ganje, 1970), and 1 to 5 µg/g have been added in regions more distant than 5 kilometers (Nriagu, 1978). In undisturbed ecosystems, atmospheric

lead is retained by soil organic matter in the upper layer of soil surface. In cultivated soils, this lead is mixed with soil to a depth of 25 cm.

Because of the special nature of the soil reservoir, it must not be regarded as an infinite sink for lead. On the contrary, atmospheric lead which is already bound to soil will continue to pass into the grazing and detrital food chains until equilibrium is reached, whereupon the lead in all reservoirs will be elevated proportionately higher than natural background levels. This conclusion applies also to cultivated soils, where lead bound within the upper 25 cm is still within the root zone.

Few plants can survive at soil concentrations in excess of 10,000 µg/g, even under optimum conditions. Some key populations of soil microorganisms and invertebrates die off at 1000 µg/g. Herbivores, in addition to a normal diet from plant tissues, receive lead from the surfaces of vegetation in amounts that may be 10 times greater than from internal plant tissue. A diet of 2 to 8 mg/day·kg body weight seems to initiate physiological dysfunction in many vertebrates.

1.8.5 Summary

Some of the known effects, which are documented in detail in the appropriate sections, are summarized here:

(1) Plants. The basic effect of lead on plants is to stunt growth. This may be through a reduction of photosynthetic rate, inhibition of respiration, cell elongation, or root development, or premature senescence. Some genetic effects have been reported. All of these effects have been observed in isolated cells or in hydroponically-grown plants in solutions comparable to 1-2 mg lead/g soil moisture. These concentrations are well above those normally found in any ecosystem except near smelters or roadsides. Terrestrial plants take up lead from the soil moisture and most of this lead is retained by the roots. There is no evidence for foliar uptake of lead and little evidence that lead can be translocated freely to the upper portions of the plant. Soil applications of calcium and phosphorus may reduce the uptake of lead by roots.

(2) Animals. Lead affects the central nervous system of animals and their ability to synthesize red blood cells. Blood concentrations above 0.4 mg/g (40 µg/dl) can cause observable clinical symptoms in domestic animals. Calcium and phosphorus can reduce the intestinal absorption of lead.

(3) Microorganisms. There is evidence that lead at environmental concentrations occasionally found near roadsides and smelters (10,000-40,000 mg/g dw) can eliminate populations of bacteria and fungi on leaf surfaces and in soil. Many of those microorganisms play key roles in the decomposition food chain. It is likely that the microbial populations are replaced by

others of the same or different species, perhaps less efficient at decomposing organic matter. There is also evidence that microorganisms can mobilize lead by making it more pheric particles. This lead becomes a part of the nutrient medium of plants and the diet of animals. All ecosystems receive lead from the atmosphere.

Perhaps the most subtle effect of lead is on ecosystems. The normal flow of energy through the decomposer food chain may be interrupted, the composition of communities may shift toward more lead-tolerant populations, and new biogeochemical pathways may be opened, as lead flows into and throughout the ecosystem. The ability of an ecosystem to compensate for atmospheric lead inputs, especially in the presence of other pollutants such as acid precipitation, depends not so much on factors of ecosystem recovery, but on undiscovered factors of ecosystem stability. Recovery implies that inputs of the perturbing pollutant have ceased and that the pollutant is being removed from the ecosystem. In case of lead, the pollutant is not being eliminated from the system nor are the inputs ceasing. Terrestrial ecosystems will never return to their original, pristine levels of lead concentrations.

1.9 QUANTITATIVE EVALUATION OF LEAD AND BIOCHEMICAL INDICES OF LEAD EXPOSURE IN PHYSIOLOGICAL MEDIA

The sine qua non of a complete understanding of a toxic agent's effects on an organism, e.g., dose-effect relationships, is quantitative measurement of either that agent in some biological medium or a physiological parameter associated with exposure to the agent. Quantitative analysis involves a number of discrete steps, all of which contribute to the overall reliability of the final analytical result: sample collection and shipment, laboratory handling, instrumental analysis, and criteria for internal and external quality control.

From a historical perspective, it is clear that the definition of "satisfactory analytical method" for lead has been steadily changing as new and more sophisticated equipment becomes available and understanding of the hazards of pervasive contamination along the analytical course increases. The best example of this is the use of the definitive method for lead analysis, isotope-dilution mass spectrometry in tandem with "ultra-clean" facilities and sampling methods, to demonstrate conclusively not only the true extent of anthropogenic input of lead to the environment over the years but also the relative limitations of most of the methods for lead measurement used today.

1.9.1 Determinations of Lead in Biological Media

The low levels of lead in biological media, even in the face of excessive exposure, and the fact that sampling of such media must be done against a backdrop of pervasive lead contamination, necessitates that samples be carefully collected and handled. Blood lead sampling is

best done by venous puncture and collection into low-lead tubes after careful cleaning of the puncture site. The use of finger puncture as an alternative method of sampling should be avoided, if feasible, given the risk of contamination associated with the practice in industrialized areas. While collection of blood onto filter paper enjoyed some popularity in the past, paper deposition of blood requires special correction for hematrocrit/hemoglobin level.

Urine sample collection requires the use of lead-free containers as well as addition of a bacteriocide. If feasible, 24-hour sampling is preferred to spot collection. Deciduous teeth vary in lead content both within and across type of dentition. Thus a specific tooth type should be uniformly obtained for all study subjects and, if possible, more than a single sample should be obtained from each subject.

Measurements of lead in blood. Many reports over the years have purported to offer satisfactory analysis of lead in blood and other biological media, often with severe inherent limitations on accuracy and precision, meager adherence to criteria for accuracy and precision, and a limited utility across a spectrum of analytical applications. Therefore, it is only useful to discuss "definitive" and, comparatively speaking, "reference" methods presently used.

In the case of lead in biological media, the definitive method is isotope-dilution mass spectrometry (IDMS). The accuracy and unique precision of IDMS arise from the fact that all manipulations are on a weight basis involving simple procedures, and measurements entail only lead isotope ratios and not the absolute determinations of the isotopes involved, greatly reducing instrumental corrections and errors. Reproducible results to a precision of one part in 10^4-10^5 are routine with appropriately designed and competently operated instrumentation. Although this methodology is still not recognized in many laboratories, it was the first breakthrough, in tandem with "ultra-clean" procedures and facilities, to definitive methods for indexing the progressive increase in lead contamination of the environment over the centuries. Given the expense, required level of operator expertise, and time and effort involved for measurements by IDMS, this methodology mainly serves for analyses that either require extreme accuracy and precision, e.g., geochronometry, or for the establishment of analytical reference material for general testing purposes or the validation of other methodologies.

While the term "reference method" for lead in biological media cannot be rigorously applied to any procedures in popular use, the technique of atomic absorption spectrometry in its various configurations or the electrochemical method, anodic stripping voltammetry, come closest to meriting the designation. Other methods that are generally applied in metal analyses are either limited in sensitivity or are not feasible for use on theoretical grounds for lead analysis.

Atomic absorption spectrometry (AAS) as applied to analysis of whole blood generally involves flame or flameless micromethods. One macromethod, the Hessel procedure, still enjoys

some popularity. Flame microanalysis, the Delves cup procedure, applied to blood lead appears to have an operational sensitivity of about 10 μg Pb/dl blood and a relative precision of approximately 5 percent in the range of blood lead seen in populations in industrialized areas. The flameless, or electrothermal, method of AAS enhances sensitivity about 10-fold, but precision can be more problematical because of chemical and spectral interferences.

The most widely used and sensitive electrochemical method for lead in blood is anodic stripping voltammetry (ASV). For most accurate results, chemical wet ashing of samples must be carried out, although this process is time-consuming and requires the use of lead-free reagents. The use of metal exchange reagents has been employed in lieu of the ashing step to liberate lead from binding sites, although this substitution is associated with less precision. For the ashing method, relative precision is approximately 5 percent. In terms of accuracy and sensitivity, it appears that there are problems at low levels, e.g., 5 μg/dl or below, particularly if samples contain elevated copper levels.

Lead in plasma. Since lead in whole blood is virtually all confined to the erythrocyte, plasma levels are quite low and it appears that extreme care must be employed to reliably measure plasma levels. The best method for such measurement is IDMS, in tandem with ultra-clean facility use. Atomic absorption spectrometry is satisfactory for comparative analyses across a range of relatively high whole blood values.

Lead in teeth. Lead measurement in teeth has involved either whole tooth sampling or analysis of specific regions, such as primary or circumpulpal dentine. In either case, samples must be solublized after careful surface cleaning to remove contamination; solubilization is usually accompanied by either wet ashing directly or ashing subsequent to a dry ashing step.

Atomic absorption spectrometry and anodic stripping have been employed more frequently for such determinations than any other method. With AAS, the high mineral content of teeth argues for preliminary isolation of lead via chelation-extraction. The relative precision of analysis for within-run measurement is around 5-7 percent, with the main determinant of variance in regional assay being the initial isolation step. One change from the usual methods for such measurement is the *in situ* measurement of lead by X-ray fluorescence spectrometry in children. Lead measured in this fashion allows observation of on-going lead accumulation, rather than waiting for exfoliation.

Lead in hair. Hair as an exposure indicator for lead offers the advantages of being non-invasive and a medium of indefinite stability. However, there is still the crucial problem of external surface contamination, which is such that it is still not possible to state that any cleaning protocol reliably differentiates between external and internally deposited lead.

Studies that demonstrate a correlation between increasing hair lead and increasing severity of a measured effect probably support arguments for hair being an external indicator of

exposure. It is probably also the case, then, that such measurement, using cleaning protocols that have not been independently validated, will overstate the relative accumulation of "internal" hair lead in terms of some endpoint and will also underestimate the relative sensitivity of changes in internal lead content with exposure. One consequence of this would be, for example, an apparent threshold for a given effect in terms of hair lead which is significantly above the actual threshold. Because of these concerns, hair is best used with the simultaneous measurement of blood lead.

Lead in urine. Analysis of lead in urine is complicated by the relatively low levels of the element in this medium as well as the complex mixture of mineral elements present. Urine lead levels are most useful and also somewhat easier to determine in cases of chelation mobilization or chelation therapy, where levels are high enough to permit good precision and dilution of matrix interference.

Samples are probably best analyzed by prior chemical wet ashing, using the usual mixture of acids. Both anodic stripping voltammetry and atomic absorption spectrometry have been applied to urine analysis, with the latter more routinely used and usually with a chelation/extraction step.

Lead in other tissues. Bone samples require cleaning procedures for removal of muscle and connective tissue and chemical solubilization prior to analysis. Methods of analysis are comparatively limited and it appears that flameless atomic absorption spectrometry is the technique of choice.

Lead measurements in bone, in vivo, have been reported with lead workers, using x-ray fluorescence analysis and a radioisotopic source for excitation. One problem with this approach with moderate lead exposure is the detection limit, approximately 20 ppm. Soft organ analysis poses a problem in terms of heterogeneity of lead distribution within an organ, e.g., brain and kidney. In such cases, regional sampling or homogenization must be carried out. Both flame and flameless atomic absorption spectrometry appear to be satisfactory for soft tissue analysis and are the most widely used.

Quality assurance procedures in lead analyses. In terms of available information, the major focus in establishing quality control protocols for lead has involved whole blood measurements. Translated into practice, quality control revolves around steps employed within the laboratory, using a variety of internal checks, and the further reliance on external checks, such as a formal continuing multi-laboratory proficiency testing program.

Within the laboratory, quality assurance protocols can be divided into start-up and routine procedures, the former involving establishment of detection limits, within-run and between-run precision, analytical recovery, and comparison with some reference technique within or outside the laboratory. The reference method is assumed to be accurate for the particular level of lead in some matrix at a particular point in time. Correlation with such a

method at a satisfactory level, however, may simply indicate that both methods are equally inaccurate but performing with the same level of precision proficiency. More preferable is the use of certified samples having lead at a level established by the definitive method.

For blood lead, the Centers for Disease Control periodically survey overall accuracy and precision of methods used by reporting laboratories. In terms of overall accuracy and precision, one such survey found that anodic stripping voltammetry as well as the Delves cup and extraction variations of atomic absorption spectrometry performed better than other procedures. These results do not mean that a given laboratory cannot perform better with a particular technique; rather, such data are of assistance for new facilities choosing among methods.

Of particular value to laboratories carrying out blood lead analysis are the external quality assurance programs at both the state and federal levels. The most comprehensive proficiency testing program is that carried out by the Centers for Disease Control, USPHS. This program actually consists of two subprograms, one directed at facilities involved in lead poisoning prevention and screening (Center for Environmental Health) and the other concerned with laboratories seeking certification under the Clinical Laboratories Improvement Act of 1967 as well as under regulations of the Occupational Safety and Health Administration's (OSHA) Laboratory Improvement Program Office. Overall, the proficiency testing programs have served their purpose well, judging from the relative overall improvements in reporting laboratories over the years of the programs' existence. In this regard, OSHA criteria for laboratory certification require 8 of 9 samples be correctly analyzed for the previous quarter. This level of required proficiency reflects the ability of a number of laboratories to actually perform at this level.

1.9.2 Determination of Erythrocyte Porphyrin (Free Erythrocyte Protoporphyrin, Zinc Protoporphyrin)

With lead exposure, there is an accumulation of erythrocyte protoporphyrin IX, owing to impaired placement of divalent iron to form heme. Divalent zinc occupies the place of the native iron. Depending upon the method of analysis, either metal-free erythrocyte porphyrin or zinc protoporphyrin (ZPP) is measured, the former arising from loss of zinc in the chemical manipulation. Virtually all methods now in use for EP analysis exploit the ability of the porphyrin to undergo intense fluorescence when excited by ultraviolet light. Such fluorometric methods can be further classified as wet chemical micromethods or direct measuring fluorometry using the hematofluorometer. Owing to the high sensitivity of such measurement, relatively small blood samples are required, with liquid samples or blood collected on filter paper.

The most common laboratory or wet chemical procedures now in use represent variations of several common chemical procedures: (1) treatment of blood samples with a mixture of ethyl

acetate/acetic acid followed by a repartitioning into an inorganic acid medium, or (2) solubilization of a blood sample directly into a detergent/buffer solution at a high dilution. Quantification has been done using protoporphyrin, coproporphyrin, or zinc protoporphyrin IX plus pure zinc ion. The levels of precision for these laboratory techniques vary somewhat with the specifics of analysis. The Piomelli method has a coefficient of variation of 5 percent, while the direct ZPP method using buffered detergent solution is higher and more variable.

The recent development of the hematofluorometer has made it possible to carry out EP measurements in high numbers, thereby making population screening feasible. Absolute calibration is necessary and requires periodic adjustment of the system using known concentrations of EP in reference blood samples. Since these units are designed for oxygenated blood, i.e., capillary blood, use of venous blood requires an oxygenation step, usually a moderate shaking for several minutes. Measurement of low or moderate levels of EP can be affected by interference with bilirubin. Competently employed, the hematofluorometer appears to be reasonably precise, showing a total coefficient of variation of 4.11-11.5 percent. While the comparative accuracy of the unit has been reported to be good relative to the reference wet chemical technique, a very recent study has shown that commercial units carry with them a significant negative bias, which may lead to false negatives in subjects having only moderate EP elevation. Such a bias in accuracy has been difficult to detect in existing EP proficiency testing programs. It appears that, by comparision to wet methods, the hematofluorometer should be restricted to field use rather than becoming a substitute in the laboratory for chemical measurement, and field use should involve periodic split-sample comparison testing with the wet method.

1.9.3 Measurement of Urinary Coproporphyrin

Although EP measurement has largely supplanted the use of urinary coproporphyrin analysis (CP-U) to monitor excessive lead exposure in humans, this measurement is still of value in that it reflects active intoxication. The standard analysis is a fluorometric technique, whereby urine samples are treated with buffer, and an oxidant (iodine) is added to generate CP from its precursor. The CP-U is then partitioned into ethyl acetate and re-extracted with dilute hydrochloric acid. The working curve is linear below 5 µg CP/dl urine.

1.9.4 Measurement of Delta-Aminolevulinic Acid Dehydrase Activity

Inhibition of the activity of the erythrocyte enzyme, delta-aminolevulinic acid dehydrase (ALA-D), by lead is the basis for using such activity in screening for excessive lead exposure. A number of sampling and sample handling precautions attend such analysis. Since zinc

(II) ion will offset the degree of activity inhibition by lead, blood collecting tubes must have extremely low zinc content. This essentially rules out the use of rubber-stoppered blood tubes. Enzyme stability is such that the activity measurement is best carried out within 24 hours of blood collection. Porphobilinogen, the product of enzyme action, is light-labile and requires the assay be done in restricted light. Various procedures for ALA-D measurement are based on measurement of the level of the chromophoric pyrrole (approximately 555 nm) formed by condensation of the porphobilinogen with p-dimethylaminobenzaldehyde.

In the European Standardized Method for ALA-D activity determination, blood samples are hemolyzed with water, ALA solution added, followed by incubation at 37°C, and the reaction terminated by a solution of mercury (II) in trichloroacetic acid. Filtrates are treated with modified Ehrlich's reagent (p-dimethylaminobenzaldehyde) in trichloroacetic/perchloroacetic acid mixture. Activity is quantified in terms of micromoles ALA/min/liter erythrocytes.

One variation in the above procedure is the initial use of a thiol agent, such as dithiothreotol, to reactivate the enzyme, giving a measure of the full native activity of the enzyme. The ratio of activated/unactivated activity vs. blood lead levels accomodates genetic differences between individuals.

1.9.5 Measurement of Delta-Aminolevulinic Acid in Urine and Other Media

Levels of delta-aminolevulinic acid (δ-ALA) in urine and plasma increase with elevated lead exposure. Thus, measurement of this metabolite, generally in urine, provides an index of the level of lead exposure. ALA content of urine samples (ALA-U) is stable for about two weeks or more with sample acidification and refrigeration. Levels of ALA-U are adjusted for urine density or expressed per unit creatinine. If feasible, 24-hour collection is more desirable than spot sampling.

Virtually all the various procedures for ALA-U measurement employ preliminary isolation of ALA from the balance of urine constituents. In one method, further separation of ALA from the metabolite aminoacetone is done. Aminoacetone can interfere with colorimetric measurement. ALA is recovered, condensed with a beta-dicarbonyl compound, e.g., acetyl acetone, to yield a pyrrole intermediate. This intermediate is then reacted with p-dimethylaminobenzaldehyde in perchloric/acetic acid, followed by colorimetric reading at 553 nm. In one variation of the basic methodology, ALA is condensed with ethyl acetoacetate directly and the resulting pyrrole extracted with ethyl acetate. Ehrlich's reagent is then added as in other procedures and the resulting chromophore measured spectrophotometrically.

Measurement of ALA in plasma is much more difficult than in urine, since plasma ALA is at nanogram/milliter levels. In one gas-liquid chromatographic procedure, ALA is isolated from plasma, reacted with acetyl acetone and partitioned into a solvent that also serves for pyrolytic methylation of the involatile pyrrole in the injector port of the chromatograph, making

the derivative more volatile. For quantification, an interval standard, 6-amino-5-oxohexanoic acid, is used. While the method is more involved, it is more specific than the older colorimetric technique.

1.9.6 Measurement of Pyrimidine-5'-Nucleotidase Activity

Erythrocyte pyrimidine-5'-nucleotidase (Py5N) activity is inhibited with lead exposure. Presently two different methods are used for assaying the activity of this enzyme. The older method is quite laborious in time and effort, whereas the more recent approach is shorter but uses radioisotopes and radiometric measurement.

In the older method, heparinized venous blood is filtered through cellulose to separate erythrocytes from platelets and leukocytes. Cells are then freeze-fractured and the hemolysates dialyzed to remove nucleotides and other phosphates. This dialysate is then incubated in the presence of a nucleoside monophosphate and cofactors, the enzyme reaction being terminated by treatment with trichloroacetic acid. The inorganic phosphate isolated from added substrate is measured colorimetrically as the phosphomolybdic acid complex.

In the radiometric assay, hemolysates obtained as before are incubated with pure ^{14}C-CMP. By addition of a barium hydroxide/zinc sulfate solution, proteins and unreacted nucleotide are precipitated, leaving labeled cytidine in the supernatant. Aliquots are measured for ^{14}C activity in a liquid scintillation counter. This method shows a good correlation with the earlier technique.

1.10 METABOLISM OF LEAD

Toxicokinetic parameters of lead absorption, distribution, retention, and excretion connecting external environmental lead exposure to various adverse effects are discussed in this section. Also considered are various influences on these parameters, e.g., nutritional status, age, and stage of development.

A number of specific issues in lead metabolism by animals and humans merit special focus and these include:

1. How does the developing organism from gestation to maturity differ from the adult in toxicokinetic response to lead intake?

2. What do these differences in lead metabolism portend for relative risk for adverse effects?

3. What are the factors that significantly change the toxicokinetic parameters in ways relevant to assessing health risk?

4. How do the various interrelationships among body compartments for lead translate to assessment of internal exposure and changes in internal exposure?

1.10.1 Lead Absorption in Humans and Animals

The amounts of lead entering the bloodstream via various routes of absorption are influenced not only by the levels of the element in a given medium but also by various physical and chemical parameters and specific host factors, such as age and nutritional status.

Respiratory absorption of lead. The movement of lead from ambient air to the bloodstream is a two-part process: deposition of some fraction of inhaled air lead in the deeper part of the respiratory tract and absorption of the deposited fraction. For adult humans, the deposition rate of particulate airborne lead as likely encountered by the general population is around 30-50 percent, with these rates being modified by such factors as particle size and ventilation rates. It also appears that essentially all of the lead deposited in the lower respiratory tract is absorbed, so that the overall absorption rate is governed by the deposition rate, i.e., approximately 30-50 percent. Autopsy results showing no lead accumulation in the lung indicate quantitative absorption of deposited lead.

All of the available data for lead uptake via the respiratory tract in humans have been obtained with adults. Respiratory uptake of lead in children, while not fully quantifiable, appears to be comparatively greater on a body weight basis, compared to adults. A second factor influencing the relative deposition rate in children has to do with airway dimensions. One report has estimated that the 10-year-old child has a deposition rate 1.6- to 2.7-fold higher than the adult on a weight basis.

It appears that the chemical form of the lead compound inhaled is not a major determinant of the extent of alveolar absorption of lead. While experimental animal data for quantitative assessment of lead deposition and absorption for the lung and upper respiratory tract are limited, available information from the rat, rabbit, dog, and nonhuman primate support the findings that respired lead in humans is extensively and rapidly absorbed.

Gastrointestinal absorption of lead. Gastrointestinal absorption of lead mainly involves lead uptake from food and beverages as well as lead deposited in the upper respiratory tract, which is eventually swallowed. It also includes ingestion of non-food material, primarily in children via normal mouthing activity and pica. Two issues of concern with lead uptake from the gut are the comparative rates of such absorption in developing vs. adult organisms, including humans, and how the relative bioavailability of lead affects such uptake.

By use of metabolic balance and isotopic (radioisotope or stable isotope) studies, various laboratories have provided estimates of lead absorption in the human adult on the order of 10-15 percent. This rate can be significantly increased under fasting conditions to 45

percent, compared to lead ingested with food. The latter figure also suggests that beverage lead is absorbed to a greater degree since much beverage ingestion occurs between meals.

The relationship of the chemical/biochemical form of lead in the gut to absorption rate has been studied, although interpretation is complicated by the relatively small amounts given and the presence of various components in food already present in the gut. In general, however, chemical forms of lead or their incorporation into biological matrices seems to have a minimal impact on lead absorption in the human gut. Several studies have focused on the question of differences in gastrointestinal absorption rates for lead between children and adults. It would appear that such rates for children are considerably higher than for adults: 10-15 percent for adults vs. approximately 50 percent for children. Available data for the absorption of lead from non-food items such as dust and dirt on hands are limited, but one study has estimated a figure of 30 percent. For paint chips, a value of about 17 percent has been estimated.

Experimental animal studies show that, like humans, the adult absorbs much less lead from the gut than the developing animal. Adult rats maintained on ordinary rat chow absorb 1 percent or less of the dietary lead. Various animal species studies make it clear that the newborn absorbs a much greater amount of lead than the adult, supporting studies showing this age dependency in humans. Compared to an absorption rate of approximately 1 percent in adult rats, the rat pup has a rate 40-50 times greater. Part, but not most, of the difference can be ascribed to a difference in dietary composition. In nonhuman primates, infant monkeys absorb 65-85 percent of lead from the gut, compared to 4 percent for the adults.

The bioavailability of lead in the gastrointestinal (GI) tract as a factor in its absorption has been the focus of a number of experimental studies. These data show that: (1) lead in a number of forms is absorbed about equally, except for the sulfide; (2) lead in dirt and dust and as different chemical forms is absorbed at about the same rate as pure lead salts added to the diet; (3) lead in paint chips undergoes significant uptake from the gut; and 4) in some cases, physical size of particulate lead can affect the rate of GI absorption.

Percutaneous absorption of lead. Absorption of inorganic lead compounds through the skin is of much less significance than through the respiratory and gastrointestinal routes. This is in contrast to the case with lead alkyls (See Section 1.10.6). One recent study using human volunteers and ^{203}Pb-labeled lead acetate showed that under normal conditions, absorption approaches 0.06 percent.

Transplacental transfer of lead. Lead uptake by the human and animal fetus readily occurs, such transfer going on by the 12th week of gestation in humans, with increasing fetal uptake throughout development. Cord blood contains significant amounts of lead, correlating with but somewhat lower than maternal blood lead levels. Evidence for such transfer, besides

lead content of cord blood, includes fetal tissue analyses and reduction in maternal blood lead during pregnancy. There also appears to be a seasonal effect on the fetus, summer-born children showing a trend toward higher blood lead levels than those born in the spring.

1.10.2 Distribution of Lead in Humans and Animals

In this subsection, the distributional characteristics of lead in various portions of the body--blood, soft tissue, calcified tissue, and the "chelatable" or potentially toxic body burden--are discussed as a function of such variables as exposure history and age.

1.10.2.1 Lead in Blood. More than 99 percent of blood lead is associated with the erythrocyte in humans under steady-state conditions, but it is the very small fraction transported in plasma and extracellular fluid that provides lead to the various body organs. Most (~ 50 percent) of erythrocyte lead is bound within the cell, primarily associated with hemoglobin (particularly HbA_2), with approximately 5 percent bound to a 10,000-dalton fraction, 20 percent to a heavier molecule, and 25 percent to lower weight species.

Whole blood lead in daily equilibrium with other compartments in adult humans appears to have a biological half-time of 25-28 days and comprises about 1.9 mg in total lead content. Human blood lead responds rather quickly to abrupt changes in exposure. With increased lead intake, blood lead achieves a new value in approximately 40-60 days, while a decrease in exposure may be associated with variable new blood values, depending upon the exposure history. This dependence presumably reflects lead resorption from bone. With age, furthermore, there appears to be little change in blood lead during adulthood. Levels of lead in blood of children tend to show a peaking trend at 2-3 years of age, probably due to mouthing activity, followed by a decline. In older children and adults, levels of lead are sex-related, females showing lower levels than men even at comparable levels of exposure.

In plasma, lead is virtually all bound to albumin and only trace amounts to high weight globulins. It is not possible to state which binding form constitutes an "active" fraction for movement to tissues. The most recent studies of the erythrocyte-plasma relationship in humans indicate that there is an equilibrium between these blood compartments, such that levels in plasma rise with levels in whole blood.

1.10.2.2 Lead Levels in Tissues. Of necessity, various relationships of tissue lead to exposure and toxicity in humans must generally be obtained from autopsy samples. Limitations on such data include questions of how samples represent lead behavior in the living population, particularly with reference to prolonged illness and disease states. The adequate characterization of exposure for victims of fatal accidents is a problem, as is the fact that such studies are cross-sectional in nature, with different age groups assumed to have had similar exposure in the past.

Soft tissues. After age 20, most soft tissues in humans do not show age-related changes, in contrast to bone. Kidney cortex shows increase in lead with age which may be associated with formation of nuclear inclusion bodies. Absence of lead accumulation in most soft tissues is due to a turnover rate for lead which is similar to that in blood.

Based on several autopsy studies, it appears that soft tissue lead content for individuals not occupationally exposed is generally below 0.5 μg/g wet weight, with higher values for aorta and kidney cortex. Brain tissue lead level is generally below 0.2 ppm wet weight with no change with increasing age, although the cross-sectional nature of these data would make changes in low brain lead levels difficult to discern. Autopsy data for both children and adults indicate that lead is selectively accumulated in the hippocampus, a finding that is also consistent with the reginal distribution in experimental animals.

Comparisons of lead levels in soft tissue autopsy samples from children with results from adults indicate that such values are lower in infants than in older children, while children aged 1-16 years had levels comparable to adult women. In one study, lead content of brain regions did not materially differ for infants and older children compared to adults. Complicating these data somewhat are changes in tissue mass with age, although such changes are less than for the skeletal system.

Subcellular distribution of lead in soft tissue is not uniform, with high amounts of lead being sequestered in the mitochondria and nucleus. Nuclear accumulation is consistent with the existence of lead-containing nuclear inclusions in various species and a large body of data demonstrating the sensitivity of mitochondria to injury by lead.

Mineralizing tissue. Lead becomes localized and accumulates in human calcified tissues, i.e., bones and teeth. This accumulation in humans begins with fetal development and continues to approximately 60 years of age. The extent of lead accumulation in bone ranges up to 200 mg in men ages 60-70 years, while in women lower values have been measured. Based upon various studies, approximately 95 percent of total body lead is lodged in the bones of human adults, with uptake distributed over trabecular and compact bone. In the human adult, bone lead is both the most inert and largest body pool, and accumulation can serve to maintain elevated blood lead levels years after exposure, particularly occupational exposure, has ended.

Compared to the human adult, 73 percent of body lead is lodged in the bones of children, which is consistent with other information that the skeletal system of children is more metabolically active than in the adult. While the increase in bone lead across childhood is modest, about 2-fold if expressed as concentration, the total accumulation rate is actually 80-fold, taking into account a 40-fold increase in skeletal mass. To the extent that some significant fraction of total bone lead in children and adults is relatively labile, it is more appropriate in terms of health risk for the whole organism to consider the total accumulation rather than just changes in concentration.

The traditional view that the skeletal system was a "total" sink for body lead (and by implication a biological safety feature to permit significant exposure in industrialized populations) never did accord with even older information on bone physiology, e.g., bone remodelling, and is now giving way to the view that there are at least several bone compartments for lead, with different mobility profiles. It would appear, then, that "bone lead" may be more of an insidious source of long-term internal exposure than a sink for the element. This aspect of the issue is summarized more fully in the next section. Available information from studies of such subjects as uranium miners and human volunteers ingesting stable isotopes indicates that there is a relatively inert bone compartment for lead, having a half-time of several decades, and a rather labile compartment which permits an equilibrium between bone and tissue lead.

Tooth lead also increases with age at a rate proportional to exposure and roughly proportional to blood lead in humans and experimental animals. Dentine lead is perhaps the most responsive component of teeth to lead exposure since it is laid down from the time of eruption until shedding. It is this characteristic which underlies the utility of dentine lead levels in assessing long-term exposure.

Chelatable lead. Mobile lead in organs and systems is potentially more active toxicologically in terms of being available to biological sites of action. Hence, this fraction of total body lead burden is a more significant predictor of imminent toxicity. In reality, direct measurement of such a fraction in human subjects would not be possible. In this regard, "chelatable" lead, measured as the extent of plumburesis in response to administration of a chelating agent, is now viewed as the most useful probe of undue body burden in children and adults.

A quantitative description of the inputs to the body lead fraction that is chelant-mobilizable is difficult to fully define, but it most likely includes a labile lead compartment within bone as well as in soft tissues. Support for this view includes: (1) the age dependency of chelatable lead, but not lead in blood or soft tissues; (2) evidence of removal of bone lead in chelation studies with experimental animals; (3) in vitro studies of lead mobilization in bone organ explants under closely defined conditions; (4) tracer modelling estimates in human subjects; and (5) the complex nonlinear relationship of blood lead and lead intake through various media. Data for children and adults showing a logarithmic relationship of chelatable lead to blood lead and the phenomenon of "rebound" in blood lead elevation after chelation therapy regimens (without obvious external re-exposure) offer further support.

Animal studies. Animal studies have been of help in sorting out some of the relationships of lead exposure to in vivo distribution of the element, particularly the impact of skeletal lead on whole body retention. In rats, lead administration results in an initial increase in soft tissues, followed by loss from soft tissue via excretion and transfer to bone.

Lead distribution appears to be relatively independent of dose. Other studies have shown that lead loss from organs follows first-order kinetics except for bone, and the skeletal system in rats and mice is the kinetically rate-limiting step in whole-body lead clearance.

The neonatal animal seems to retain proportionally higher levels of tissue lead compared to the adult and manifests slow decay of brain lead levels while showing a significant decline over time in other tissues. This appears to be the result of enhanced lead entry into the brain because of a poorly developed blood-brain barrier system as well as enhanced body retention of lead by young animals.

The effects of such changes as metabolic stress and nutritional status on body redistribution of lead have been noted. Lactating mice, for example, are known to demonstrate tissue redistribution of lead, specifically bone lead resorption with subsequent transfer of both lead and calcium from mother to pups.

1.10.3 Lead Excretion and Retention in Humans and Animals

Human studies. Dietary lead in humans and animals that is not absorbed passes through the gastrointestinal tract and is eliminated with feces, as is the fraction of air lead that is swallowed and not absorbed. Lead entering the bloodstream and not retained is excreted through the renal and GI tracts, the latter via biliary clearance. The amounts excreted through these routes are a function of such factors as species, age, and exposure characteristics.

Based upon the human metabolic balance data and isotope excretion findings of various investigators, it appears that short-term lead excretion in adult humans amounts to 50-60 percent of the absorbed fraction, with the balance moving primarily to bone and some fraction (approximately half) of this stored amount eventually being excreted. This overall retention figure of 25 percent necessarily assumes that isotope clearance reflects that for body lead in all compartments. The rapidly excreted fraction has a biological half-time of 20-25 days, similar to that for lead removal from blood. This similarity indicates a steady rate of lead clearance from the body. In terms of partitioning of excreted lead between urine and bile, one study indicates that the biliary clearance is about 50 percent that of renal clearance.

Lead is accumulated in the human body with age, mainly in bone, up to around 60 years of age, when a decrease occurs with changes in intake as well as in bone mineral metabolism. As noted earlier, the total amount of lead in long-term retention can approach 200 mg, and even much higher in the case of occupational exposure. This corresponds to a lifetime average retention rate of 9-10 μg Pg/day. Within shorter time frames, however, retention will vary considerably due to such factors as development, disruption in the individuals' equilibrium with lead intake, and the onset of such states as osteoporosis.

The age dependency of lead retention/excretion in humans has not been well studied, but most of the available information indicates that children, particularly infants, retain a significantly higher amount of lead. While autopsy data indicate that pediatric subjects at isolated points in time actually have a lower fraction of body lead lodged in bone, a full understanding of longer-term retention over childhood must consider the exponential growth rate occurring in a child's skeletal system over the time period for which bone lead concentrations have been gathered. This parameter itself represents a 40-fold mass increase. This significant skeletal growth rate has an impact on an obvious question: if children take in more lead on a body weight basis than adults, absorb and retain more lead than adults, and show only modest elevations in blood lead compared to adults in the face of a more active skeletal system, where does the lead go? A second factor is the assumption that blood lead in children relates to body lead burden in the same quantitative fashion as in adults, an assumption that remains to be adequately proven.

Animal studies. In rats and other experimental animals, both urinary and fecal excretion appear to be important routes of lead removal from the organism; the relative partitioning between the two modes is species- and dose-dependent. With regard to species differences, biliary clearance of lead in the dog is but 2 percent of that for the rat, while such excretion in the rabbit is 50 percent that of the rat.

Lead movement from laboratory animals to their offspring via milk constituents is a route of excretion for the mother as well as an exposure route for the young. Comparative studies of lead retention in developing vs. adult animals, e.g., rats, mice, and non-human primates, make it clear that retention is significantly greater in the young animal. These observations support those studies showing greater lead retention in children. Some recent data indicate that a differential retention of lead in young rats persists into the post-weaning period, calculated as either uniform dosing or uniform exposure.

1.10.4 Interactions of Lead with Essential Metals and Other Factors

Toxic elements such as lead are affected in their toxicokinetic or toxicological behavior by interactions with a variety of biochemical factors such as nutrients.

Human studies. In humans the interactive behavior of lead and various nutritional factors is expressed most significantly in young children, with such interactions occurring against a backdrop of rather widespread deficiencies in a number of nutritional components. Various surveys have indicated that deficiency in iron, calcium, zinc, and vitamins are widespread among the pediatric population, particularly the poor. A number of reports have documented the association of lead absorption with suboptimal nutritional states for iron and calcium, reduced intake being associated with increased lead absorption.

Animal studies. Reports of lead-nutrient interactions in experimental animals have generally described such relationships for a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the recent data are for calcium, iron, phosphorus, and vitamin D. Many studies have established that diminished dietary calcium is associated with increased blood and soft tissue lead content in such diverse species as the rat, pig, horse, sheep, and domestic fowl. The increased body burden of lead arises from both increased GI absorption and increased retention, indicating that the lead-calcium interaction operates at both the gut wall and within body compartments. Lead appears to traverse the gut via both passive and active transfer, involves transport proteins normally operating for calcium transport, and is taken up at the site of phosphorus, not calcium, absorption.

Iron deficiency is associated with an increase in lead of tissues and increased toxicity, an effect which is expressed at the level of lead uptake by the gut wall. In vitro studies indicate an interaction through receptor binding competition at a common site. This probably involves iron-binding proteins. Similarly, dietary phosphate deficiency enhances the extent of lead retention and toxicity via increased uptake of lead at the gut wall, both lead and phosphate being absorbed at the same site in the small intestine. Results of various studies of the resorption of phosphate along with lead as one further mechanism of elevation of tissue lead have not been conclusive. Since calcium plus phosphate retards lead absorption to a greater degree than simply the sums of the interactions, it has been postulated that an insoluble complex of all these elements may be the basis of this retardation.

Unlike the inverse relationship existing for calcium, iron, and phosphate vs. lead uptake, vitamin D levels appear to be directly related to the rate of lead absorption from the GI tract, since the vitamin stimulates the same region of the duodenum where lead is absorbed. A number of other nutrient factors are known to have an interactive relationship with lead:

1. Increases in dietary lipids increase the extent of lead absorption, with the extent of the increase being highest with polyunsaturates and lowest with saturated fats, e.g., tristearin.

2. The interactive relationship of lead and dietary protein is not clearcut, and either suboptimal or excess protein intake increases lead absorption.
3. Certain milk components, particularly lactose, also greatly enhance lead absorption in the nursing animal.

4. Zinc deficiency promotes lead absorption, as does reduced dietary copper.

1.10.5 Interrelationships of Lead Exposure with Exposure Indicators and Tissue Lead Burdens

There are three issues involving lead toxicokinetics which bear importantly on the characterization of relationships between lead exposure and its toxic effects: (1) the temporal

characteristics of internal indices of lead exposure; (2) the biological aspects of the relationship of lead in various environmental media to various indicators of internal exposure; and (3) the relationship of various internal indicators of exposure to target tissue lead burdens.

Temporal characteristics of internal indicators of lead exposure. The biological half-time for newly absorbed lead in blood appears to be of the order of weeks or several months, so that this medium reflects relatively recent exposure. If recent exposure is fairly representative of exposure over a considerable period of time, e.g., exposure of lead workers, then blood lead is more useful than for cases where exposure is intermittent across time, as is often the case of pediatric lead exposure. Accessible mineralized tissue, such as shed teeth, extend the time frame back to years of exposure, since teeth accumulate lead with age and as a function of the extent of exposure. Such measurements are, however, retrospective in nature, in that identification of excessive exposure occurs after the fact and thus limits the possibility of timely medical intervention, exposure abatement, or regulatory policy concerned with ongoing control strategies.

Perhaps the most practical solution to the dilemma posed by both tooth and blood lead analyses is in situ measurement of lead in teeth or bone during the time when active accumulation occurs, e.g., in 2 to 3-year-old children. Available data using X-ray fluorescence analysis suggest that such approaches are feasible and can be reconciled with such issues as acceptable radiation hazard risk to subjects.

Biological aspects of external exposure-internal indicator relationships. It is clear from a reading of the literature that the relationship of lead in relevant media for human exposure to blood lead is curvilinear when viewed over a relatively broad range of blood lead values. This implies that the unit change in blood lead per unit intake of lead in some medium varies across this range of exposure, with comparatively smaller blood lead changes as internal exposure increases.

Given our present knowledge, such a relationship cannot be taken to mean that body uptake of lead is proportionately lower at higher exposure, for it may simply mean that blood lead becomes an increasingly unreliable measure of target tissue lead burden with increasing exposure. While the basis of the curvilinear relationship remains to be identified, available animal data suggest that it does not reflect exposure-dependent absorption or excretion rates.

Internal indicator-tissue lead relationships. In living human subjects, it is not possible to determine directly tissue lead burdens or how these relate to adverse effects in target tissues; some accessible indicator, e.g., lead in a medium such as blood or a biochemical surrogate of lead such as EP, must be employed. While blood lead still remains the only practical measure of excessive lead exposure and health risk, evidence continues to accumulate that

such an index has limitations in either reflecting tissue lead burdens or changes in such tissues with changes in exposure.

At present, the measurement of plumburesis associated with challenge by a single dose of a lead chelating agent such as $CaNa_2EDTA$ is considered the best indicator of the mobile, potentially toxic fraction of body lead. Chelatable lead is logarithmically related to blood lead, such that incremental increase in blood lead is associated with an increasingly larger increment of mobilizable lead. The problems associated with this logarithmic relationship may be seen in studies of children and lead workers in whom moderate elevation in blood lead can disguise levels of mobile body lead. This reduces the margin of protection against severe intoxication. The biological basis of the logarithmic relationship between chelatable lead and blood lead rests, in large measure, with the existence of a sizable bone lead compartment that is mobile enough to undergo chelation removal and, hence, potentially mobile enough to move into target tissues.

Studies of the relative mobility of chelatable lead over time indicate that, in former lead workers, removal from exposure leads to a protracted washing out of lead (from bone resorption of lead) to blood and tissues, with preservation of a bone burden amenable to subsequent chelation. Studies with children are inconclusive, since the one investigation directed to this end employed pediatric subjects who all underwent chelation therapy during periods of severe lead poisoning. Animal studies demonstrate that changes in blood lead with increasing exposure do not agree with tissue uptake in a time-concordant fasion, nor does decrease in blood lead with reduced exposure signal a similar decrease in target tissue, particularly in the brain of the developing organism.

1.10.6 Metabolism of Lead Alkyls

The lower alkyl lead components used as gasoline additives, tetraethyl lead (TEL) and tetramethyl lead (TML), may themselves poise a toxic risk to humans. In particular, there is among children a problem of sniffing leaded gasoline.

Absorption of lead alkyls in humans and animals. Human volunteers inhaling labeled TEL and TML show lung deposition rates for the lead alkyls of 37 and 51 percent, respectively, values which are similar to those for particulate inorganic lead. Significant portions of these deposited amounts were eventually absorbed. Respiratory absorption of organolead bound to particulate matter has not been specifically studied as such.

While specific data for the GI absorption of lead alkyls in humans and animals are not available, their close similarity to organotin compounds, which are quantitatively absorbed, would argue for extensive GI absorption. In contrast to inorganic lead salts, the lower lead alkyls are extensively absorbed through the skin and animal data show lethal effects with percutaneous uptake as the sole route of exposure.

Biotransformation and tissue distribution of lead alkyls. The lower lead alkyls TEL and TML undergo monodealkylation in the liver of mammalian species via the P-450-dependent monooxygenase enzyme system. Such transformation is very rapid. Further transformation involves conversion to the dialkyl and inorganic lead forms, the latter accounting for the effects on heme biosynthesis and erythropoiesis observed in alkyl lead intoxication. Alykl lead is rapidly cleared from blood, shows a higher partitioning into plasma than inorganic lead with triethyl lead clearance being more rapid than the methyl analog.

Tissue distribution of alkyl lead in humans and animals primarily involves the trialkyl metabolites. Levels are highest in liver, followed by kidney, then brain. Of interest is the fact that there are detectable amounts of trialkyl lead from autopsy samples of human brain even in the absence of occupational exposure. In humans, there appear to be two tissue compartments for triethyl lead, having half-times of 35 and 100 days.

Excretion of lead alkyls. With alkyl lead exposure, excretion of lead through the renal tract is the main route of elimination. The chemical forms being excreted appear to be species-dependent. In humans, trialkyl lead in workers chronically exposed to alkyl lead is a minor component of urine lead, approximately 9 percent.

1.11 ASSESSMENT OF LEAD EXPOSURES AND ABSORPTION IN HUMAN POPULATIONS

Chapter 11 describes the effect of exposure of human populations to lead in their environment. The effect discussed is a change in an internal exposure index that follows changes in external exposures. The index of internal lead exposure most frequently cited is blood lead levels, but other indices such as levels of lead in tooth and bone are also presented. Blood lead level estimates the body's recent exposure to environmental lead, while teeth and bone lead levels represent cumulative exposures.

Measurement of lead in blood has been accomplished via a succession of analytical procedures over the years. With these changes in technology there has been increasing recognition of the importance of controlling for contamination in the sampling and analytical procedures. These advances as well as the institution of external quality control programs have resulted in markedly improved analytic results. A generalized improvement in analytic results across many laboratories occurred during Federal Fiscal Years 1977-1979.

The main discussion of scientific evidence in Chapter 11 is structured to achieve four main objectives:

(1) Elucidate patterns of absorbed lead in U.S. populations and identify important demographic covariates.

(2) Characterize relationships between external and internal exposures by exposure medium.

(3) Define the relative contributions of various sources of lead in the environment to total internal exposure.

(4) Identify specific sources of lead which result in increased internal exposure levels.

A question of major interest in understanding environmental pollutants is the extent to which current ambient exposures exceed background levels. Ancient Nubians samples (dated 3300-2900 B.C.) averaged 0.6 μg lead/g for bone and 0.9 μg lead/g for teeth. More recent Peruvian Indian samples (12th Century) had teeth lead levels of 13.6 μg/g. Contemporary Alaskan Eskimo samples had a mean of 56.0 μg/g, while Philadelphia samples had a mean of 188.3 μg/g. These data suggest an increasing pattern of lead absorption.

Several studies have looked at the blood lead levels in current remote populations such as natives in a remote (far from industrialized regions) section of Nepal where the lead content of the air samples proved to be less than the detection limit, 0.004 $\mu g/m^3$ (Piomelli et al., 1980). The geometric mean blood lead for this population was 3.4 μg/dl. Adult males had a geometric mean of 3.8 μg/dl and adult females, 2.9 μg/dl. Children had a geometric mean blood lead of 3.5 μg/dl.

1.11.1 Levels of Lead and Demographic Covariates in U.S. Populations

The National Center for Health Statistics has provided the best currently available picture of blood lead levels among United States residents as part of the second National Health and Nutrition Examination Study (NHANES II) conducted from February, 1976 to February, 1980 (Mahaffey et al., 1980; McDowell et al., 1981; Annest et al., 1982). The national estimates are based on 9933 persons whose blood lead levels ranged from 2.0 to 66.0 μg/dl. The median blood lead for the entire U.S. population is 13.0 μg/dl.

Age appears to be one of the most important demographic covariates of blood lead levels. Blood lead levels in children are generally higher than those in non-occupationally exposed adults. Childred aged 24-36 months tend to have the highest blood lead levels. The age trends in blood lead levels for children under 10 years old, as seen in three studies are presented in Figure 1-13. Blood lead levels in non-occupationally exposed adults may increase slightly with age due to skeletal lead accumulation.

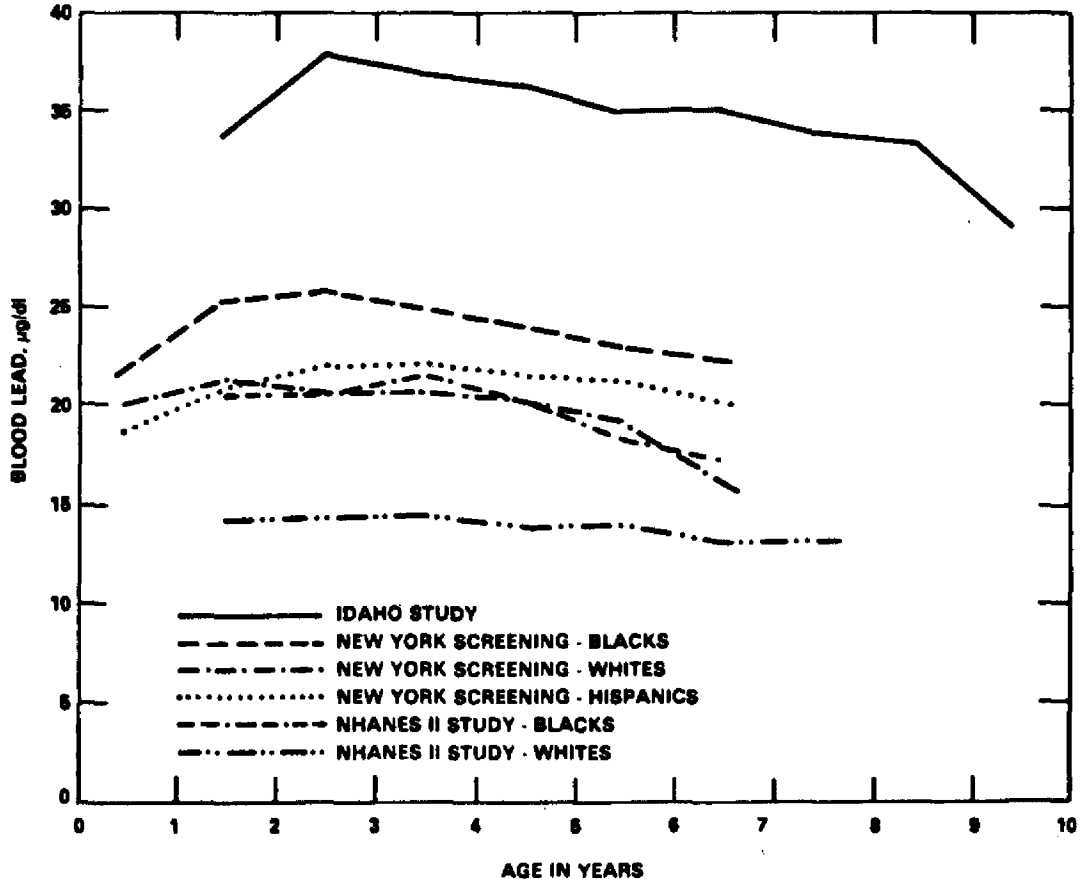

Figure 1-13. Geometric mean blood lead levels by race and age for younger children in the NHANES II study, and the Kellogg/Silver Valley and New York Childhood Screening Studies.

Sex has a differential impact on blood lead levels depending on age. No significant difference exists between males and females less than seven years of age. Males above the age of seven generally have higher blood lead levels than females. Race also plays a role, in that blacks have higher blood lead levels than either whites or Hispanics. The reason for this has yet to be totally disentangled from exposure.

Blood lead levels also seem to increase with degree of urbanization. Data from NHANES II show that blood lead levels in the United States, averaged from 1976 to 1980, increase from a geometric mean of 11.9 µg/dl in rural populations to 12.8 µg/dl in urban populations less than one million and increase again to 14.0 µg/dl in urban populations of one million or more. (see Table 1-9).

Recent U.S. blood lead levels show that a downward has trend occurred consistently across race, age, and geographic location. The downward pattern commenced in the early part of the 1970's and has continued into 1980. The downward trend has occurred from a shift in the entire distribution and not just via a truncation in high blood lead levels. This consistency suggests a general causative factor and attempts have been made to identify the causative element. Reduction in lead emitted from the combustion of leaded gasoline is a prime candidate, but as yet no causal relationship has been definitively established.

Blood lead data from the NHANES II study demonstrates well, on a nationwide basis, a significant downward trend over time (Annest et al., 1982). Mean blood lead levels dropped from 15.8 µg/dl during the first six months of the survey to 10.0 µg/dl during the last six months. Mean values from these national data presented in six months increments from February 1976 to February 1980 are displayed in Figure 1-14.

Billick and colleagues have analyzed the results of blood lead screening programs conducted by the City of New York. Geometric mean blood lead levels decreased for all three racial groups and for almost all age groups in the period 1970-76. Figure 1-15 shows that the downward trend covers the entire range of the frequency distribution of blood lead levels. The decline in blood lead levels showed seasonal variability, but the decrease in time was consistent for each season.

Gause et al. (1977) present data from Newark, New Jersey, which reinforces the findings of Billick and coworkers. Gause et al. studied the levels of blood lead among 5- and 6-year-old children tested by the Newark Board of Education during the academic years 1973-74, 1974-75, and 1975-76. Blood lead levels declined markedly during this 3-year period.

Rabinowitz and Needleman (1982) report a more recent study of umbilical cord blood lead levels from 11,837 births between April, 1979 and April, 1981 in the Boston area. The overall mean blood lead concentration was 6.56 ± 3.19 (standard deviation) with a range from 0.0 to 37.9 µg/dl. A downward trend in umbilical cord blood lead levels was noted over the two years of the study.

TABLE 1-9. WEIGHTED GEOMETRIC MEAN BLOOD LEAD LEVELS FROM NHANES II SURVEY BY DEGREE OF URBANIZATION OF PLACE OF RESIDENCE IN THE U.S. BY AGE AND RACE, UNITED STATES 1976-80

Race and age	Degree of urbanization		
	Urban, ≥1 million	Urban, <1 million	Rural
All races	Geometric mean (μg/dl)		
All ages	14.0	12.8	11.9
6 months-5 years	16.8	15.3	13.1
6-17 years	13.1	11.7	10.7
18-74 years	14.1	12.9	12.2
Whites			
All ages	14.0	12.5	11.7
6 months-5 years	15.6	14.4	12.7
6-17 years	12.7	11.4	10.5
18-74 years	14.3	12.7	12.1
Blacks			
All ages	14.4	14.7	14.4
6 months-5 years	20.9	19.3	16.4
6-17 years	14.6	13.6	12.9
18-74 years	13.9	14.7	14.9

Source: Annest et. al., 1982.

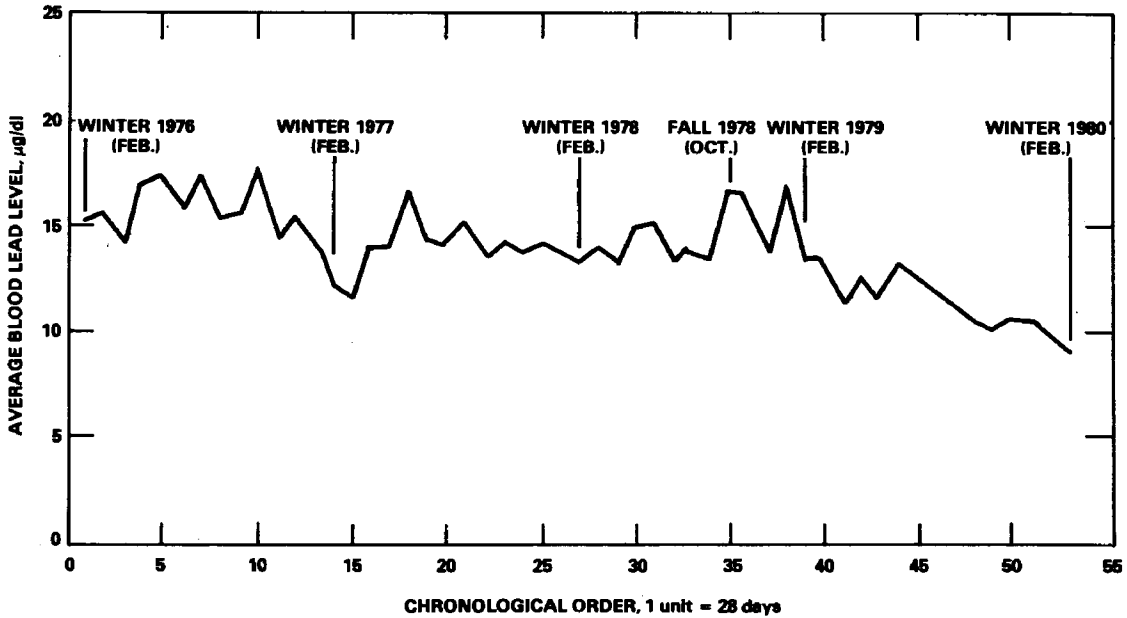

Figure 1-14. Average blood lead levels of U.S. population 6 months—74 years, United States, February 1976—February 1980, based on dates of examination of NHANES II examinees with blood lead determinations.

Source: Annest et al. (1983).

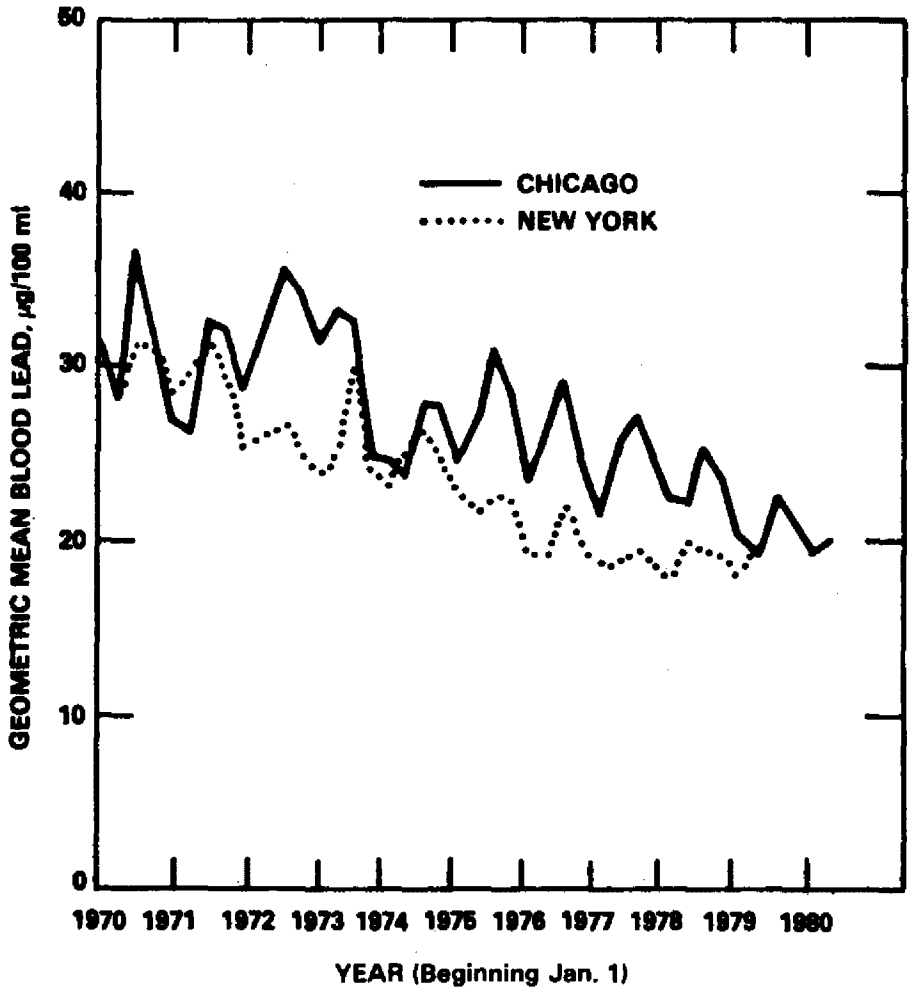

Figure 1-15. Time dependence of blood lead for blacks, aged 24 to 35 months, in New York City and Chicago.

Source: Adapted from Billick (1982).

The importance of the distributional form of blood lead levels is that the distributional form determines which measure of central tendency (arithmetic mean, geometric mean, median) is most appropriate. It is even more important in estimating percentiles in the tail of the distribution, which represents those individuals at highest risk exposure-wise.

Based on the examination of the NHANES II data, as well as the results of several other papers, it appears that the lognormal distribution is the most appropriate for describing the distribution of blood lead levels in homogeneous populations with nearly constant external exposure levels. The lognormal distribution appears to fit well across the entire range of the distribution, including the right tail of the distribution. Blood lead levels, examined on a population basis, have similarly skewed distributions. Blood lead levels from a population thought to be homogenous in terms of demographic and lead exposure characteristics approximately follow a lognormal distribution. The geometric standard deviation for four different studies are shown in Table 1-10. The values, including analytic error, are about 1.4 for children and possibly somewhat smaller for adults. This allows an estimation of the upper tail of the blood lead distribution, the group at higher risk.

Results obtained from the NHANES II study show that urban children generally have the highest blood lead levels of any non-occupationally exposed population group. Furthermore, black urban children have significantly higher blood lead levels than white urban children. Several case control studies of children have shown that blood lead levels are related to hand lead levels, house dust levels, lead in outside soil, interior paint lead level, and history of pica. These factors are discussed in greater detail in the following sections.

1.11.2 Blood Lead vs. Inhaled Air Lead Relationships

The mass of data on the relationship of blood lead level and air lead exposure is complicated by the need for reconciling the results of experimental and observational studies. Further, the process of determining the best form of the statistical relationship deduced is problematic due to the lack of consistency of range of the air lead expsoures encountered in the various studies.

Because the main purpose of this document is to examine relationships of lead in air and lead in blood under ambient conditions, EPA has chosen to emphasize the results of studies most appropriately addressing this issue. A summary of the most appropriate studies appears in Table 1-11. At air lead exposures of 3 $\mu g/m^3$ or less, there is no statistically significant difference between curvilinear and linear blood lead inhalation relationships. At air lead exposures of 10 $\mu g/m^3$ or more either nonlinear or linear relationships can be fitted. Thus a reasonably consistent picture emerges in which the blood lead-air lead relationship by direct inhalation was approximately linear in the range of normal ambient exposures (0.1 - 2.0 $\mu g/m^3$.) Therefore EPA has fitted linear relationships to blood lead levels in the studies

TABLE 1-10. SUMMARY OF POOLED GEOMETRIC STANDARD DEVIATIONS AND ESTIMATED ANALYTIC ERRORS

Study	Pooled Geometric Standard Deviations				Estimated Analytic Error
	Inner City Black Children	Inner City White Children	Adult Females	Adult Males	
NHANES II	1.37	1.39	1.36[a]	1.40[a]	0.021
N.Y. Childhood Screening Study	1.41	1.42	-	-	(b)
Tepper-Levin	-	-	1.30	-	0.056[c]
Azar et al.	-	-	-	1.29	0.042[c]

Note: To calculate an estimated person-to-person GSD, compute Exp $[(\ln(GSD))^2 - \text{Analytic Error})^{\frac{1}{2}}]$.

[a]pooled across areas of differing urbanization.

[b]not known, assumed to be similar to NHANES II.

[c]taken from Lucas (1981).

to be described with the explicit understanding that the fitted relationships are intended only to describe changes in blood due to modest changes in air lead among individuals whose blood lead levels do not exceed 30 μg/dl.

The blood-lead inhalation slope estimates vary appreciably from one subject to another in experimental and clinical studies, and from one study to another. The weighted slope and standard error estimates from the Griffin study (1.75 ± 0.35) were combined with those calculated similarly for the Rabinowitz study in (2.14 ± 0.47) and the Kehoe study in Table 11-20 (1.25 ± 0.35 setting DH = 0), yielding a pooled weighted slope estimate of 1.64 ± 0.22 μg/dl per μg/m^3 There are some advantages in using these experimental studies on adult males, but certain deficiencies are acknowledged. The Kehoe study exposed subjects to a wide range of exposure levels while in the exposure chamber, but did not control air lead exposures outside the chamber. The Griffin study provided reasonable control of air lead exposure during the experiment, but difficulties in defining the non-inhalation baseline for blood lead (especially in the important experiment at 3 μg/m^3) add much uncertainty to the estimate. The Rabinowitz study controlled well for diet and other factors and, since they used stable lead isotope tracers, they had no baseline problem. However, the actual air lead exposure of these subjects outside the metabolic ward was not well determined.

TABLE 1-11. SUMMARY OF BLOOD INHALATION SLOPES (β)
μg/dl per μg/m^3

Population	Study	Study Type	N	Slope	Model Sensitivity* of Slope
Children	Angle and McIntire (1979) Omaha, NE	Population	1074	1.92	(1.40-4.40)[1,2,3]
	Roels et al. (1980) Belgium	Population	148	2.46	(1.55-2.46)[1,2]
	Yankel et al. (1977); Walter et al. (1980) Idaho	Population	879	1.52	(1.07-1.52)[1,2,3]
Adult Male	Azar et al. (1975). Five groups	Population	149	1.32	(1.08-1.59)[2,3]
	Griffin et al. (1975) NY prisoners	Experiment	43	1.75	(1.52-3.38)[4]
	Gross (1979)	Experiment	6	1.25	(1.25-1.55)[2]
	Rabinowitz et al. (1973, 1976, 1977)	Experiment	5	2.14	(2.14-3.51)[5]

*Selected from among the most plausible statistically equivalent models. For nonlinear models, slope at 1.0 μg/m^3.

[1]Sensitive to choice of other correlated predictors such as dust and soil lead.

[2]Sensitive to linear vs. nonlinear at low air lead.

[3]Sensitive to age as a covariate.

[4]Sensitive to baseline changes in controls.

[5]Sensitive to assumed air lead exposure.

Among population studies, only the Azar study provides a slope estimate in which individual air lead exposures are known. However, there was no control of dietary lead intake or other factors that affect blood lead levels, and slope estimates assuming only air lead and location as covariables (1.32 ± 0.38) are not significantly different from the pooled experimental studies.

There are no experimental inhalation studies on adult females or on children. The inhalation slope for women should be roughly the same as that for men, assuming proportionally

smaller air intake and blood volume. The assumption of proportional size is less plausible for children. Slope estimates for children from population studies are used in which some other important covariates of lead absorption were controlled or measured, e.g., age, sex, dust exposure in the environment or on the hands. Inhalation slopes were estimated for the studies of Angle and McIntire (1.92 ± 0.60), Roels (2.46 ± 0.58), and Yankel et al. (1.53 ± 0.064). The standard error of the Yankel study is extremely low and a weighted pooled slope estimate for children would reflect essentially that study alone. In this case the small standard error estimate is attributable to the very large range of air lead exposures of children in the Silver Valley (up to 22 $\mu g/m^3$). The relationship is in fact not linear, but increases more rapidly in the upper range of air lead exposures. The slope estimate at lower air lead concentrations may not wholly reflect uncertainty about the shape of the curve at higher concentrations. The unweighted mean slope of the three studies and its standard error estimate are 1.97 ± 0.39.

To summarize the situation briefly: (1) The experimental studies at lower air lead levels (3.2 $\mu g/m^3$ or less) and lower blood levels (typically 30 µg/dl or less) have linear blood lead inhalation relationships with slopes β_i of 0-3.6 for most subjects. A typical value of 1.64 ± 0.22 may be assumed for adults. (2) Population cross-sectional studies at lower air lead and blood lead levels are approximately linear with slopes β of 0.8-2.0. (3) Cross-sectional studies in occupational exposure situations in which air lead levels are higher (much above 10 $\mu g/m^3$) and blood lead levels are higher (above 40 µg/dl) show a much more shallow linear blood lead inhalation relation. The slope β is in the range of 0.03-0.2. (4) Cross-sectional and experimental studies at levels of air lead somewhat above the higher ambient exposures (9-36 $\mu g/m^3$) and blood leads of 30-40 µg/dl can be described either by a nonlinear relationship with decreasing slope or by a linear relationship with intermediate slope, approximately $\beta = 0.5$. Several biological mechanisms for these differences have been discussed (Hammond et al., 1981; O'Flaherty et al., 1982; Chamberlain, 1983; Chamberlain and Heard, 1981). Since no explanation for the decrease in steepness of the blood lead inhalation response to higher air lead levels has been generally accepted at this time, there is little basis on which to select an interpolation formula from low air lead to high air lead exposures. The increased steepness of the inhalation curve for the Kellogg/Silver Valley study is inconsistent with the other studies presented. It may be that smelter situations are unique and must be analyzed differently, or it may be that the curvatuve is the result of imprecise exposure estimates. (5) The blood-lead inhalation slope for children is at least as steep as that for adults, with an estimate of 1.97 ± 0.39 from three major studies. These slope estimates are based on the assumption that an equilibrium level of blood lead is achieved within a few months after exposure begins. This is only approximately true, since lead stored in the

skeleton may return to blood after some years. Chamberlain et al. (1978) suggest that long term inhalation slopes should be about 30 percent larger than these estimates. Inhalation slopes quoted here are associated with a half-life of blood lead in adults of about 30 days. O'Flaherty et al. (1982) suggest that the blood-lead half-life may increase slightly with duration of exposure, but this has not been confirmed (Kang et al., 1983).

Other studies, reviews, and analyses of the study are discussed in Section 11.4, to which the reader is referred for a detailed discussion and for a review of the key studies and their analyses.

It must not be assumed that the direct inhalation of air lead is the only air lead contribution that needs to be considered. Smelter studies allow partial assessment of the air lead contributions to soil, dust, and finger lead. Useful ecological models to study the possible propagation of lead through the food chain have not yet been developed. The direct inhalation relationship does provide useful information on changes in blood lead as responses to changes in air lead on a time scale of several months. The indirect pathways through dust and soil and through the food chain may thus delay the total blood lead response to changes in air lead, perhaps by one or more years.

1.11.3 Dietary Lead Exposures Including Water

Dietary absorption of lead varies greatly from one person to another and depends on the physical and chemical form of the carrier, on nutritional status, and on whether lead is ingested with food or between meals. These distinctions are particularly important for consumption of leaded paint, dust, and soil by children. Typical values of 10 percent absorption of ingested lead into blood have been assumed for adults and 25-50 percent for children.

It is difficult to obtain accurate dose-response relationships between blood lead levels and lead level in food or water. Dietary intake must be estimated by duplicate diets or fecal lead determinations. Water lead levels can be determined with some accuracy, but the varying amounts of water consumed by different individuals adds to the uncertainty of the estimated relationships.

Quantitative analyses relating blood lead levels and dietary lead exposures have been reported. Studies on infants provide estimates that are in close agreement. Only one individual study is available for adults; another estimate from a number of pooled studies is also available. These two estimates are in good agreement. Most of the subjects in the Sherlock et al. (1982) and United Kingdom Central Directorate on Environmental Pollution (1982) studies received quite high dietary lead levels (>300 μg/day). The fitted cube root equations give high slopes at lower dietary lead levels. On the other hand, the linear slope of the United Kingdom Central Directorate on Environmental Pollution (1982) study is probably an underestimate of the slope at lower dietary lead levels. For these reasons, the Ryu et al. (1983)

study is the most believable, although it only applies to infants. Estimates for adults should be taken from the experimental studies or calculated from assumed absorption and half-life values.

Most of the dietary intake supplements were so high that many of the subjects had blood lead concentrations much in excess of 30 µg for a considerable part of the experiment. Blood lead levels thus may not completely reflect lead exposure, due to the previously noted non-linearity of blood lead response at high exposures. The slope estimates for adult dietary intake are about 0.02 µg/dl increase in blood lead per µg/d intake, but consideration of blood lead kinetics may increase this value to about 0.04 µg/dl per µg/d intake. Such values are somewhat (about 0.05 µg/dl per µd/d) lower than those estimated from the population studies extrapolated to typical dietary intakes. The value for infants is much larger. The relationship between blood lead and water lead is not clearly defined and is often described as non-linear. Water lead intake varies greatly from one person to another. It has been assumed that children can absorb 25 to 50 percent of lead in water. Many authors chose to fit cube root models to their data, although polynomial and logarithmic models were also used. Unfortunately, the form of the model greatly influences the estimated contributions to blood lead levels from relatively low water lead concentrations.

Although there is close agreement in quantitative analyses of relationships between blood lead levels and dietary lead concentrations, there is a larger degree of variability in results of the various water lead studies. The relationship is curvilinear but its exact form is yet to be determined. At typical levels for U.S. populations the relationship appears to be linear. The only study that determines the relationship based on lower water lead values (<100 µg/l) is the Pocock et al. (1983) study. The data from this study, as well as the authors themselves, suggest that the relationship is linear for this lower range of water lead levels. Furthermore, the estimated contributions to blood lead levels from this study are quite consistent with the polynomial models from other studies. For these reasons, the Pocock et al. (1983) slope of 0.06 is considered to represent the best estimate. The possibility still exists, however, that the higher estimates of the other studies may be correct in certain situations, especially at higher water lead levels (>100 µg/l).

1.11.4 Studies Relating Lead in Soil and Dust to Blood Lead

The relationship of exposure to lead contained in soil and house dust and the amount of lead absorbed by humans, particularly children, has been the subject of a number of scientific investigations. Some of these studies have been concerned with the effects of exposures resulting from the ingestion of lead in dust (Duggan and Williams, 1977; Barltrop, 1975; Creason et al., 1975); others have concentrated on the means by which the lead in soil and

dust becomes available to the body (Sayre et al., 1974). Sayre et al. (1974) demonstrated the feasibility of house dust as a source of lead for children in Rochester, NY. Two groups of houses, one inner city and the other suburban, were chosen for the study. Lead-free sanitary paper towels were used to collect dust samples from house surfaces and the hands of children (Vostal et al., 1974). The medians for the hand and household samples were used as the cut-points in the chi-square contingency analysis. A statistically significant difference between the urban and suburban homes for dust levels was noted, as was a relationship between household dust levels and hand dust levels (Lepow et al., 1975).

Studies relating soil lead to blood lead levels are difficult to compare. The relationship obviously depends on depth of soil lead, age of the children, sampling method, cleanliness of the home, mouthing activities of the children, and possibly many other factors. Various soil sampling methods and sampling depths have been used over time; as such they may not be directly comparable and may produce a dilution effect of the major lead concentration contribution from dust, which is located primarily in the top 2 cm of the soil.

Increases in soil dust lead significantly increase blood lead in children. From several studies EPA estimates an increase of 0.6 to 6.8 µg/dl in blood lead for each increase of 1000 µg/g in soil lead concentration. The values from the Stark et al. (1982) study may represent a reasonable median estimate, i.e. about 2.0 µg/dl for each 1000 µg/dl increase in soil lead. Household dust also increases blood lead, children from the cleanest homes in the Kellogg/Silver Valley Study having 6 µg/dl less lead in blood, on average, than those from the households with the most dust.

1.11.5 Paint Lead Exposures

A major source of environmental lead exposure for many members of the general population comes from lead contained in both interior and exterior paint on dwellings. The amount of lead present, as well as its accessibility, depends upon the age of the residence (because older buildings contain paint manufactured before lead content was regulated) and the physical condition of the paint. In a survey of lead levels in 2370 randomly selected dwellings in Pittsburgh, PA (Shier and Hall, 1977), paint with high levels of lead were most frequently found in pre-1940 residences. One cannot assume, however, that high level lead paint is absent in dwellings built after 1940. In the case of the houses surveyed in Pittsburgh, about 20 percent of the residences built after 1960 have at least one surface with more than 1.5 mg/cm^2 lead. In fiscal year 1981, the U.S. Centers for Disease Control (1982), screened 535,730 children and found 21,897 with lead toxicity. Of these cases, 15,472 dwellings were inspected and 10,666 (approximately 67 percent) were found to have leaded paint.

1.11.6 Specific Source Studies

Two field investigations have attempted to derive an estimate of the amount of lead from gasoline that is absorbed by the blood of individuals. Both of these investigations used the fact that the isotopes of lead are stable and thus, the varying proportions of the isotopes present in blood and environmental samples can indicate the source of the lead. The Isotope Lead Experiment (ILE) is a massive study that attempted to utilize differing proportions of the isotopes in geologic formations to infer the proportion of lead in gasoline that is absorbed by the body. The other study utilized existing natural shifts in isotopic proportions in an attempt to do the same thing.

The ILE is a large scale community trial in which the geologic source of lead for antiknock compounds in gasoline was manipulated to change the isotopic composition of lead in the atmosphere (Garibaldi et al., 1975; Facchetti, 1979). The isotopic lead ratios obtained in the samples analyzed are displayed in Figure 1-16. It can be easily seen that the airborne particulate lead rapidly changed its isotope ratio in line with expectation. Ratios in the blood samples appeared to lag somewhat behind. Background lead isotopic ratios were 1.1603 ± 0.0028 in rural areas and 1.1609 ± 0.0015 in Turin in 1975. In Turin school children in 1977-78, a mean isotopic ratio of 1.1347 was obtained.

Preliminary analysis of the isotope ratios in air lead has allowed the estimation of the fractional contribution of gasoline in the city of Turin, in small communities within 25 km of Turin and in small communities beyond 25 km (Facchetti and Geiss, 1982). At the time of maximal use of Australian lead isotope in gasoline (1978-79), about 87.3 percent of the air lead in Turin and 58.7 percent of the air lead in the countryside was attributable to gasoline. The determination of lead isotope ratios was essentially independent of specific air lead concentrations. During that time, air lead averaged about 2.0 $\mu g/m^3$ in Turin (from 0.88 to 4.54 $\mu g/m^3$ depending on location of the sampling site), about 0.56 $\mu g/m^3$ in the nearby communities (0.30 to 0.67 $\mu g/m^3$), and about 0.30 $\mu g/m^3$ in distant locations.

Isotope ratios in the blood of 35 subjects also changed, and the fraction of lead in blood attributable to gasoline could be estimated independently of blood level concentration. The mean fraction decreased from 23.7 ± 5.4 percent in Turin to 12.5 ± 7.1 percent in the nearby countryside, and to 11.0 ± 5.8 percent in the remote countryside.

These results can be combined with the actual blood lead concentrations to estimate the fraction of the gasoline uptake that is attributable to direct inhalation and that which is not. The results are shown in Table 1-12 (based on a suggestion by Dr. Fachetti). As concluded earlier, an assumed value of β=1.6 is plausible for predicting the amount of lead absorbed into blood at air lead concentrations less than 2.0 $\mu g/m^3$. The predicted values for airborne lead derived from leaded gasoline range from 0.28 to 2.79 $\mu g/dl$ in blood due to direct inhalation. The total contribution of blood lead from gasoline is much larger, from

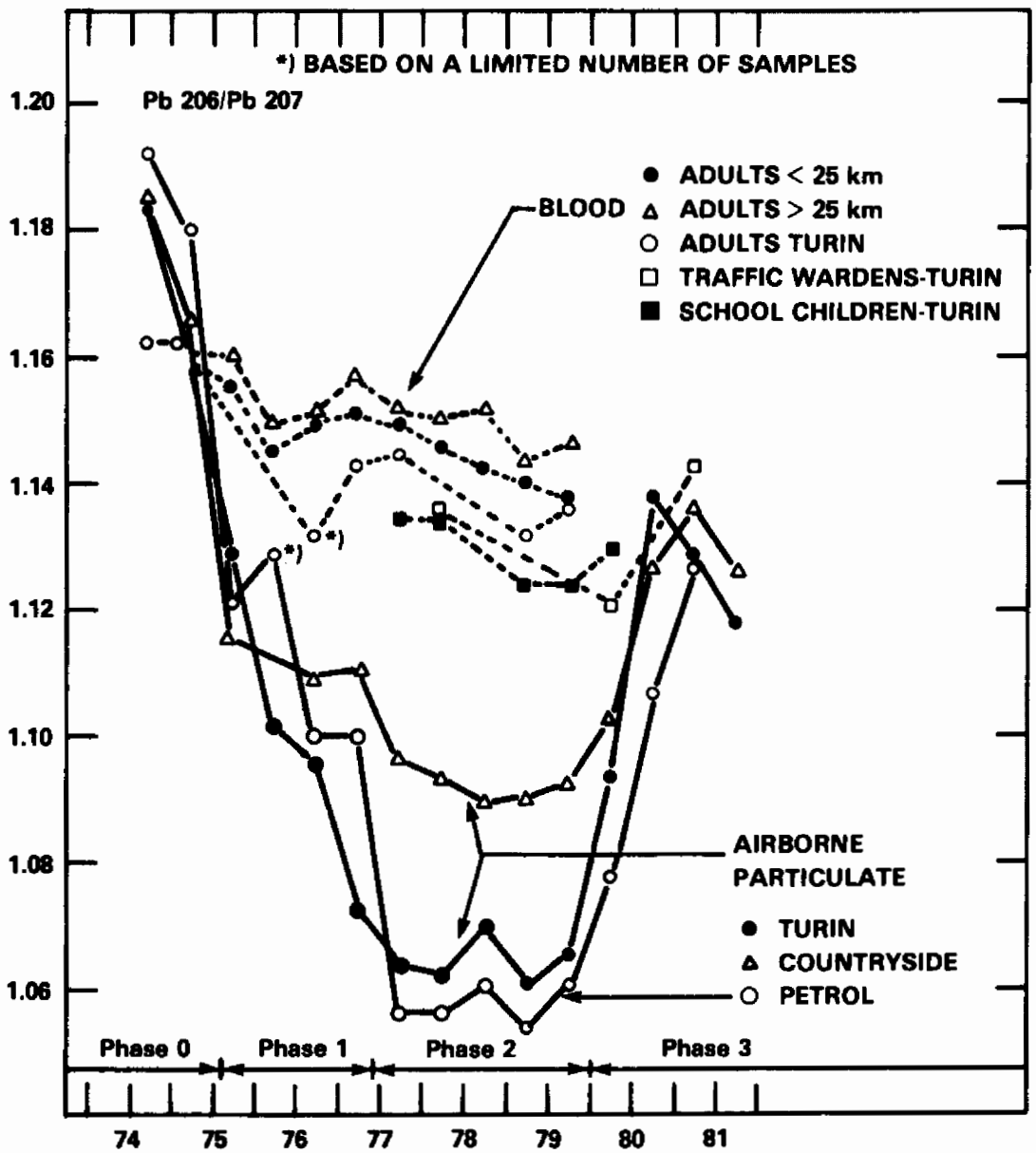

Figure 1-16. Change in Pb-206/Pb-207 ratios in petrol, airborne particulate, and blood from 1974 to 1981.

Source: Facchetti and Geiss (1982).

TABLE 1-12. ESTIMATED CONTRIBUTION OF LEADED GASOLINE TO BLOOD LEAD BY INHALATION AND NON-INHALATION PATHWAYS

Location	Air Lead Fraction From Gasoline[a]	Air Lead Conc.[b] ($\mu g/m^3$)	Lead Fraction From Gasoline[c]	Mean Blood Lead Conc.[d] ($\mu g/dl$)	Blood Lead From Gasoline[e] ($\mu g/dl$)	Lead From Gasoline In Air[f] ($\mu g/dl$)	Non-Inhaled Lead From Gasoline[g] ($\mu g/dl$)	Estimated Fraction Gas-Lead Inhalation[h]
Turin	0.873	2.0	0.237	21.77	5.16	2.79	2.37	0.54
<25 km	0.587	0.56	0.125	25.06	3.13	0.53	2.60	0.17
>25 km	0.587	0.30	0.110	31.78	3.50	0.28	3.22	0.08

[a]Fraction of air lead in Phase 2 attributable to lead in gasoline.

[b]Mean air lead in Phase 2, $\mu g/m^3$.

[c]Mean fraction of blood lead in Phase 2 attributable to lead in gasoline.

[d]Mean blood lead concentration in Phase 2, $\mu g/dl$.

[e]Estimated blood lead from gasoline = (c) x (d)

[f]Estimated blood lead from gas inhalation = β x (a) x (b), β = 1.6.

[g]Estimated blood lead from gas, non-inhalation = (f)-(e)

[h]Fraction of blood lead uptake from gasoline attributable to direct inhalation = (f)/(e)

Data from Facchetti and Geiss (1982), pp. 52-56.

3.50 to 5.16 $\mu g/dl$, suggesting that the non-inhalation total contribution of gasoline increases from 2.37 $\mu g/dl$ in Turin to 2.60 $\mu g/dl$ in the near region and 3.22 $\mu g/dl$ in the more distant region. The non-inhalation sources include ingestion of dust and soil lead and lead in food and drinking water. Efforts are being made to quantify their magnitude. The average direct inhalation of lead in the air from gasoline is 8-17 percent of the total intake attributable to gasoline in the countryside and an estimated 68 percent in the city of Turin.

Manton (1977) conducted a long term study of 10 subjects whose blood lead isotopic composition was monitored for comparison with the isotopic composition of the air they breathed. Manton had observed that the ratio of lead 206/204 in the air varied with seasons in Dallas, Texas; therefore, the ratio of those isotopes should vary in the blood. By comparing the observed variability, estimates could then be made of the amount of lead in air that is absorbed by the blood. From the Manton study it is estimated that between 7 and 41 percent of the blood lead in study subjects in Dallas results from airborne lead. Additionally these data provide a means of estimating the indirect contribution of air lead to blood lead. By one estimate, only 10-20 percent of the total airborne contributions in Dallas is from direct inhalation.

In summary, the direct inhalation pathway accounts for only a fraction of the total air lead concentration of blood, the direct inhalation contribution being on the order of 12-23 percent of the total uptake of lead attributable to gasoline, using Stephen's assumptions. This is consistent with estimates from the ILE study.

Another approach was taken in New York City. Billick et al. (1979) presented several possible explanations for observed declines in blood lead levels (discussed earlier above) and evidence supporting and refuting each. The suggested contributing factors were the active educational and screening program of the New York City Bureau of Lead Poisoning Control, and the decrease in the amount of lead-based paint exposure as a result of rehabilitation or removal of older housing stock of changes in environmental lead exposure. Information was available only to partially evaluate the last source of lead exposure and particularly only for ambient air lead levels. Air lead measurements were available during the entire study period for only one station which was located on the west side of Manhattan at a height of 56 m. Superimposition of the air lead and blood lead levels indicated a similarity in both upward cycle and decline. The authors cautioned against overinterpretation by assuming that one air monitoring site was representative of the air lead exposure of New York City residents. With this in mind, the investigators fitted a multiple regression model to the data to try to define the important determinants of blood lead levels for this population. Age, ethnic group and air lead level were all found to be significant determinants of blood lead levels. The authors further point out the possibility of a change in the nature of the population being screened before and after 1973. They reran this regression analysis separately for years both before and after 1973. The same results were still obtained, although the exact coefficients derived varied.

Billick et al. (1980) extended their previous analysis of the data from the single monitoring site mentioned earlier. The investigators examined the possible relationship between blood lead level and the amount of lead in gasoline used in the New York City area. Figures 1-17 and 1-18 present illustrative trend lines in blood leads for blacks and Hispanics and air lead and gasoline lead, respectively. Several different measures of gasoline lead were used: (1) mid-Atlantic Coast (NY, NJ, Conn); (2) New York City plus New Jersey, and (3) New York city plus Connecticut. The lead in gasoline trend line appears to fit the blood lead trend line better than the air lead trend, especially in the summer of 1973.

1.11.7 Primary Smelters Populations

In 1972, the Centers for Disease Control studied the relationships between blood lead levels and environmental factors in the vicinity of a primary smelter emitting lead, copper, and zinc located in El Paso, Texas, that had been in operation since the late 1800's (Landrigan et al., 1975; U.S. Centers for Disease Control, 1973). Daily high volume samples

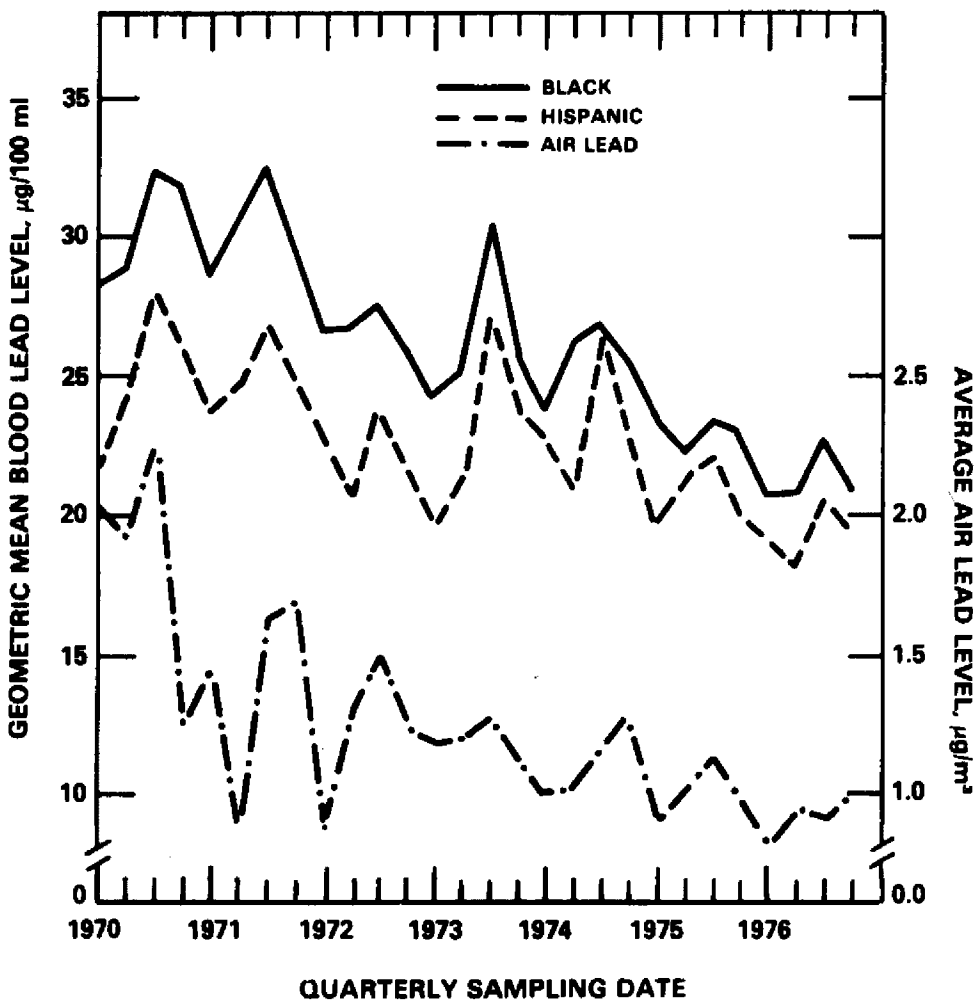

Figure 1-17. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and ambient air lead concentration versus quarterly sampling period, 1970-1976.

Source: Billick et al. (1980).

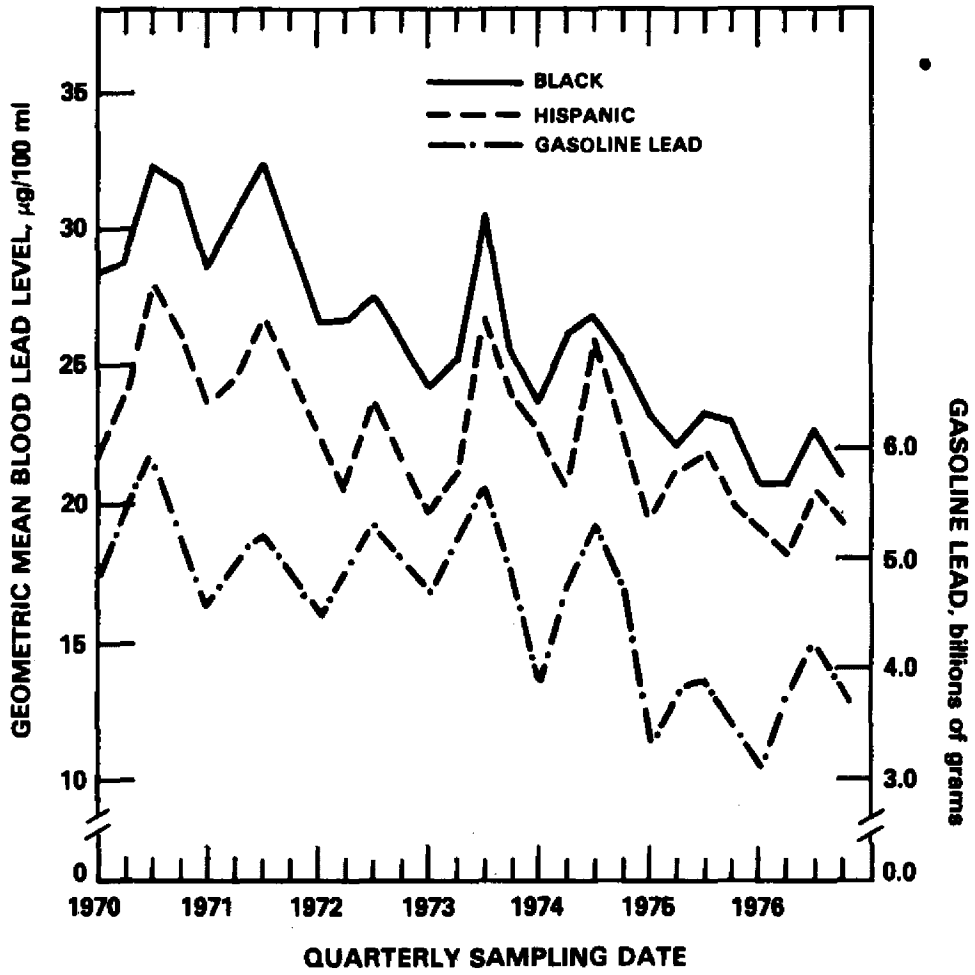

Figure 1-18. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and estimated amount of lead present in gasoline sold in New York, New Jersey, and Connecticut versus quarterly sampling period, 1970-1976.

Source: Billick et al. (1980).

collected on 86 days between February and June, 1972 averaged 6.6 μg/m^3. These air lead levels fell off rapidly with distance, reaching background values approximately 5 km from the smelter. Levels were higher downwind, however. High concentrations of lead in soil and house dusts were found, with the highest levels occurring near the smelter. The geometric means of lead content in 82 soil and 106 dust samples from the sector closest to the smelter were 1791 and 4022 μg/g, respectively. Geometric means of both soil and dust lead levels near the smelter were significantly higher than those in study sectors 2 or 3 km farther away. Sixty-nine percent of children 1- to 4-years old living near the smelter had blood lead levels <40 μg/dl, and 14 percent had blood lead levels that exceeded 60 μg/dl. Concentrations in older individuals were lower; nevertheless, 45 percent of the children 5- to 9-years old, 31 percent of the individuals 10- to 19-years old, and 16 percent of the individuals above age 19 had blood lead levels exceeding 40 μg/dl.

Cavalleri et al. (1981) studied children in the vicinity of a lead smelter and children from a control area (4 km from the smelter). Since the smelter had installed filters 8 years before the study, the older children living in the smelter area had a much higher lifetime exposure. A striking difference in blood lead levels of the exposed and control populations was observed; levels in the exposed population were almost twice that in the control population. The geometric mean for nursery school children was 15.9 and 8.2 μg/dl for exposed and control, respectively. For primary school it was 16.1 and 7.0 μg/dl. The air lead levels were between 2 to 3 μg/m^3 in the exposed and 0.56 μg/m^3 in the control cases.

1.11.8 Secondary Exposure of Children

Excessive intake and absorption of lead on the part of children can result when parents who work in a dusty environment with a high lead content bring dust home on their clothing, their shoes, or even their automobiles. Once home, their children are exposed to the high-lead content dust.

Landrigan et al. (1976) reported that the 174 children of smelter workers who live within 24 km of a smelter had significantly higher blood lead levels (a mean of 55.1 μg/dl) than 511 children of persons in other occupations who lived in the same areas (whose mean blood lead levels were 43.7 μg/dl). Other studies have documented increased lead absorption in children of families where at least one member was occupationally exposed to lead (Fischbein et al., 1980a). The occupational exposures often involved battery plant operations (Morton et al., 1982; U.S. Centers for Disease Control, 1977; Dolcourt et al., 1978, 1981; Watson et al., 1978; Ferguson et al., 1981), as well as other occupations (Snee, 1982b; Rice et al., 1978).

1.12 BIOLOGICAL EFFECTS OF LEAD EXPOSURE

1.12.1 Introduction

Lead has diverse biological effects in humans and animals. Its effects are seen at the subcellular level of organellar structures and processes as well as at the overall level of general functioning that encompasses all systems of the body operating in a coordinated, interdependent fashion.

This review seeks not only to categorize and describe the various biological effects of lead but to identify the exposure levels at which such effects occur and the mechanisms underlying them. The dose-response curve for the entire range of lead's biological effects is rather broad, with certain biochemical changes occurring at relatively low levels of exposure and perturbations in some organ systems, such as the endocrine, being obvious only at relatively high exposure levels. In terms of relative vulnerability to lead's deleterious effects, the developing organism appears to be more sensitive than the mature individual, particularly where the neurotoxic effects of lead are concerned.

1.12.2 Subcellular Effects of Lead

The biological basis of lead toxicity is its ability to bind to ligating groups in biomolecular substances crucial to various physiological functions, thereby interfering with these functions by, for example, competing with native essential metals for binding sites, inhibiting enzyme activity, and inhibiting or otherwise altering essential ion transport. These effects are modulated by: (1) the inherent stability of such binding sites for lead; (2) the compartmentalization kinetics governing lead distribution among body compartments, among tissues, and within cells; and (3) the differences in biochemical organization across cells and tissues due to their specific functions. Given the complexities introduced by items 2 and 3, it is not surprising that no single, unifying mechanism of lead toxicity across all tissues in humans and experimental animals has yet been identified.

In so far as effects of lead on activity of various enzymes are concerned, many of the available studies concern *in vitro* behavior of relatively pure enzymes with marginal relevance to various effects *in vivo*. On the other hand, certain enzymes are basic to the effects of lead at the organ or organ system level, and discussion is best reserved for such effects in sections below dealing with particular organ systems. This section is mainly concerned with organellar effects of lead, particularly those which provide some rationale for lead toxicity at higher levels of biological organization. Particular emphasis is placed on the mitochondrion, since this organelle is not only affected by lead in a number of ways but has provided the most data.

The main target organelle for lead toxicity in a variety of cell and tissue types clearly is the mitochondrion, followed probably by cellular and intracellular membranes. The mitochondrial effects take the form of structural changes and marked disturbances in mitochondrial function within the cell, particularly in energy metabolism and ion transport. These effects in turn are associated with demonstrable accumulation of lead in mitochondria, both *in vivo* and *in vitro*. Structural changes include mitochondrial swelling in a variety of cell types as well as distortion and loss of cristae, which may occur at relatively moderate levels of lead exposure. Similar changes have also been documented in lead workers across a range of exposure levels.

Uncoupled energy metabolism, inhibited cellular respiration using both succinate and nicotinamide adenine dinucleotide (NAD)-linked substrates, and altered kinetics of intracellular calcium have been demonstrated *in vivo* using mitochondria of brain and non-neural tissue. In some cases, the lead exposure level associated with such changes has been relatively moderate. Studies documenting the relatively greater sensitivity of this organelle in young vs. adult animals in terms of mitochondrial respiration have been reported. The cerebellum appears to be particularly sensitive, providing a connection between mitochondrial impairment and lead encephalopathy. Impairment by lead of mitochondrial function in the developing brain has also been consistently associated with delayed brain development, as indexed by content of various cytochromes. In the rat pup, ongoing lead exposure from birth is required for this effect to be expressed, indicating that such exposure must occur before, and is inhibitory to, the burst of oxidative metabolism activity that occurs in the young rat at 10 through 21 days postnatally.

In vivo lead exposure of adult rats has also been seen to markedly inhibit cerebral cortex intracellular calcium turnover in a cellular compartment that appears to be the mitochondrion. The effect was seen at a brain lead level of 0.4 ppm. These results are consistent with a separate study showing increased retention of calcium in the brain of lead-dosed guinea pigs. A number of reports have described the *in vivo* accumulation of lead in mitochondria of kidney, liver, spleen, and brain tissue, with one study showing that such uptake was slightly more than occurred in the nucleus. These data are not only consistent with the various deleterious effects of lead on mitochondria but are also supported by other investigations *in vitro*.

Significant decreases in mitochondrial respiration *in vitro* using both NAD-linked and succinate substrates have been observed for brain and non-neural tissue mitochondria in the presence of lead at micromolar levels. There appears to be substrate specificity in the inhibition of respiration across different tissues, which may be a factor in differential organ toxicity. Also, a number of enzymes involved in intermediary metabolism in isolated mitochondria have been observed to undergo significant inhibition of activity with lead.

A particular focus on lead's effects on isolated mitochondria has been ion transport, especially with regard to calcium. Lead movement into brain and other tissue mitochondria involves active transport, as does calcium. Recent sophisticated kinetic analyses of desaturation curves for radiolabeled lead or calcium indicate that there is striking overlap in the cellular metabolism of calcium and lead. These studies not only establish the basis of lead's easy entry into cells and cell compartments, but also provide a basis for lead's impairment of intracellular ion transport, particularly in neural cell mitochondria, where the capacity for calcium transport is 20-fold higher than even in heart mitochondria.

Lead is also selectively taken up in isolated mitochondria in vitro, including the mitochondria of synaptosomes and brain capillaries. Given the diverse and extensive evidence of lead's impairment of mitochondrial structure and function as viewed from a subcellular level, it is not surprising that these derangements are logically held to be the basis of dysfunction of heme biosynthesis, erythropoiesis, and the central nervous system. Several key enzymes in the heme biosynthetic pathway are intramitochondrial, particularly ferrochelatase. Hence, it is to be expected that entry of lead into mitochondria will impair overall heme biosynthesis, and in fact this appears to be the case in the developing cerebellum. Furthermore, the levels of lead exposure associated with entry of lead into mitochondria and expression of mitochondrial injury can be relatively moderate.

Lead exposure provokes a typical cellular reaction in human and other species that has been morphologically characterized as a lead-containing nuclear inclusion body. While it has been postulated that such inclusions constitute a cellular protection mechanism, such a mechanism is an imperfect one. Other organelles, e.g., the mitochondrion, also take up lead and sustain injury in the presence of inclusion formations. Chromosomal effects and other indices of genotoxicity in humans and animals are considered in Section 1.12.7.

In theory, the cell membrane is the first organelle to encounter lead and it is not surprising that cellular effects of lead can be ascribed to interactions at cellular and intracellular membranes in the form of distrubed ion transport. The inhibition of membrane (Na^+,K^+)-ATPase of erythrocytes as a factor in lead-impaired erythropoiesis is noted elsewhere. Lead also appears to interfere with the normal processes of calcium transport across membranes of different tissues. In peripheral cholinergic synaptosomes, lead is associated with retarded release of acetylcholine owing to a blockade of calcium binding to the membrane, while calcium accumulation within nerve endings can be ascribed to inhibition of membrane (Na^+,K^+)-ATPase.

Lysosomes accumulate in renal proximal convoluted tubule cells of rats and rabbits given lead over a range of dosing. This also appears to occur in the kidneys of lead workers and seems to represent a disturbance in normal lysosomal function, with the accumulation of lysosomes being due to enhanced degradation of proteins because of the effects of lead elsewhere within the cell.

1.12.3. Effects of Lead on Heme Biosynthesis, Erythropoiesis, and Erythrocyte Physiology in Humans and Animals

The effects of lead on heme biosynthesis are well known because of both their prominence and the large number of studies of these effects in humans and experimental animals. The process of heme biosynthesis starts with glycine and succinyl-coenzyme A, proceeds through formation of protoporphyrin IX, and culminates with the insertion of divalent iron into the porphyrin ring, thus forming heme. In addition to being a constituent of hemoglobin, heme is the prosthetic group of a number of tissue hemoproteins having variable functions, such as myoglobin, the P-450 component of the mixed function oxygenase system, and the cytochromes of cellular energetics. Hence, disturbance of heme biosynthesis by lead poses the potential for multiple-organ toxicity.

At present, the steps in the heme synthesis pathway that have been best studied with respect to lead's effects involve three enzymes: (1) stimulation of mitochondrial delta-aminolevulinic acid synthetase (ALA-S), which mediates the formation of delta-aminolevulinic acid (ALA); (2) direct inhibition of the cytosolic enzyme, delta-aminolevulinic acid dehydrase (ALA-D), which catalyzes formation of porphobilinogen from two units of ALA; and (3) inhibition of the insertion of iron (II) into protoporphyrin IX to form heme, a process mediated by the enzyme ferrochelatase.

Increased ALA-S activity has been documented in lead workers as well as lead-exposed animals, although the converse, an actual decrease in enzyme activity, has also been observed in several experimental studies using different exposure methods. It would appear, then, that enzyme activity increase via feedback derepression or that activity inhibition may depend on the nature of the exposure. In an *in vitro* study using rat liver cells in culture, ALA-S activity could be stimulated at levels as low as 5.0 μM or 1.0 μg Pb/g preparation. In the same study, increased activity was seen to be due to biosynthesis of more enzyme. The threshold for lead stimulation of ALA-S activity in humans, based upon a study using leukocytes from lead workers, appears to be about 40 μg Pb/dl. The generality of this threshold level to other tissues is dependent upon how well the sensitivity of leukocyte mitochondria mirrors that in other systems. It would appear that the relative impact of ALA-S activity stimulation on ALA accumulation at lower levels of lead exposure is considerably less than the effect of ALA-D activity inhibition: at 40 μg/dl blood lead, ALA-D activity is significantly depressed, whereas ALA-S activity only begins to be affected at that blood lead concentration.

Erythrocyte ALA-D activity is very sensitive to lead inhibition, which is reversed by reactivation of the sulfhydryl group with agents such as dithiothreitol, zinc, or zinc plus glutathione. The zinc levels employed to achieve reactivation, however, are well above normal physiological levels. Although zinc appears to offset the inhibitory effects of lead observed in human erythrocytes *in vitro* and in animal studies, lead workers exposed to both zinc and

lead do not show significant changes in the relationship of ALA-D activity to blood lead concentration when compared to workers exposed only to lead. In contrast, zinc deficiency in animals has been shown to significantly inhibit ALA-D activity, with concomitant accumulation of ALA in urine. Since zinc deficiency has also been associated with increased lead absorption in experimental studies, the possibility exists for a dual effect of such deficiency on ALA-D activity: (1) a direct effect on activity due to reduced zinc availability, as well as (2) the effect of increased lead absorption leading to further inhibition of such activity.

The activity of erythrocyte ALA-D appears to be inhibited at virtually all blood lead levels measured so far, and any threshold for this effect in either adults or children remains to be determined. A further measure of this enzyme's sensitivity to lead comes from a report noting that rat bone marrow suspensions show inhibition of ALA-D activity by lead at a level of 0.1 μg/g suspension. Inhibition of ALA-D activity in erythrocytes apparently reflects a similar effect in other tissues. Hepatic ALA-D activity was inversely correlated in lead workers with both the erythrocyte activity as well as blood lead. Of significance are the experimental animal data showing that (1) brain ALA-D activity is inhibited with lead exposure and (2) inhibition appears to occur to a greater extent in the brain of developing vs. adult animals. This presumably reflects greater retention of lead in developing animals. In the avian brain, cerebellar ALA-D activity is affected to a greater extent than that of the cerebrum and, relative to lead concentration, shows inhibition approaching that occurring in erythrocytes.

The inhibition of ALA-D activity by lead is reflected in increased levels of its substrate, ALA, in blood, urine, and tissues. In one investigation, the increase in urinary ALA was seen to be preceded by a rise in circulating levels of the metabolite. Blood ALA levels were elevated at all corresponding blood lead values down to the lowest value determined (18 μg/dl), while urinary ALA was seen to rise exponentially with blood ALA. Urinary ALA has been employed extensively as an indicator of excessive lead exposure in lead workers. The value of this measurement for diagnostic purposes in pediatric screening, however, is limited if only spot urine collection is done; more satisfactory data can be obtained in cases where 24-hour collections are feasible. A large number of independent studies have documented that there is a direct correlation between blood lead and the logarithm of urinary ALA in adult humans and children, and that the threshold is commonly accepted as being 40 μg/dl. Several studies of lead workers also indicate that the correlation of urinary ALA with blood lead continues below this value. Furthermore, one report has demonstrated that the slope of the dose-effect curve in lead workers is dependent upon the level of exposure.

The health significance of lead-inhibited ALA-D activity and accumulation of ALA at low levels of exposure has been an issue of some controversy. One view is that the "reserve capacity" of ALA-D activity is such that only high accumulations of the enzyme's substrate,

ALA, in accessible indicator media would result in significant inhibition of activity. One difficulty with this view is that it is not possible to quantify at lower levels of lead exposure the relationship of urinary ALA to levels in target tissues nor to relate the potential neurotoxicity of ALA at any level of build-up to levels in indicator media; i.e., the threshold for potential neurotoxicity of ALA in terms of blood lead may be different from the level associated with urinary accumulation.

Accumulation of protoporphyrin in the erythrocytes of individuals with lead intoxication has been recognized since the 1930s, but it has only recently been possible to quantitatively assess the nature of this effect via the development of specific, sensitive micromethods of analysis. Accumulation of protoporphyrin IX in erythrocytes is the result of impaired placement of iron (II) in the porphyrin moiety to form heme, an intramitochondrial process mediated by the enzyme ferrochelatase. In lead exposure, the porphyrin acquires a zinc ion in lieu of native iron, thus forming zinc protoporphyrin (ZPP), and is tightly bound in available heme pockets for the life of the erythrocytes. This tight sequestration contrasts with the relatively mobile non-metal, or free, erythrocyte protoporphyrin (FEP) accumulated in the congenital disorder erythropoietic protoporphyria.

Elevation of erythrocyte ZPP has been extensively documented as being exponentially correlated with blood lead in children and adult lead workers and is presently considered one of the best indicators of undue lead exposure. Accumulation of ZPP only occurs in erythrocytes formed during lead's presence in erythroid tissue, resulting in a lag of at least several weeks before such build-up can be measured. It has been shown that the level of such accumulation in erythrocytes of newly-employed lead workers continues to increase when blood lead has already reached a plateau. This would influence the relative correlation of ZPP and blood lead in workers with a short exposure history. In individuals removed from occupational exposure, the ZPP level in blood declines much more slowly than blood lead, even years after removal from exposure or after a drop in blood lead. Hence, ZPP level would appear to be a more reliable indicator of continuing intoxication from lead resorbed from bone.

The measurable threshold for the effect of lead on ZPP accumulation is affected by the relative spread of blood lead and corresponding ZPP values measured. In young children (under four years of age) the ZPP elevation typically associated with iron-deficiency anemia should be taken into account. In adults, a number of studies indicate that the threshold for ZPP elevation with respect to blood lead is approximately 25-30 µg/dl. In children 10-15 years old the threshold is about 16 µg/dl; in this age group, iron deficiency is not a factor. In one report, it was noted that children over four years of age showed the same threshold, 15.5 µg/dl, as a second group under four years old, indicating that iron deficiency was not a factor in the study. Fifty percent of the children were found to have significantly elevated EP levels (2 standard deviations [SDs] above reference mean EP) or a dose-response threshold level of 25 µg/dl.

Below 30-40 µg/dl, any assessment of the ZPP-blood lead relationship is strongly influenced by the relative analytical proficiency for measurement of both blood lead and EP. The types of statistical treatments given the data are also important. In a recent detailed statistical study involving 2004 children, 1852 of whom had blood lead values below 30 µg/dl, segmental line and probit analysis techniques were employed to assess the dose-effect threshold and dose-response relationship. An average blood lead threshold for the effect using both statistical techniques yielded a value of 16.5 µg/dl for either the full group or those subjects with blood lead levels below 30 µg/dl. The effect of iron deficiency was tested for and removed. Of particular interest was the finding that the blood lead values corresponding to EP elevations more than 1 or 2 standard deviations above the reference mean in 50 percent of the children were 28.6 or 35.7 µg Pb/dl, respectively. Hence, fully half of the children were seen to have significant elevations of EP at blood lead levels around the currently used cut-off value for undue lead exposure, 30 µg/dl. From various reports, children and adult females appear to be more sensitive to the effects of lead on EP accumulation at any given blood lead level, with children being somewhat more sensitive than adult females.

Effects of lead on ZPP accumulation and reduced heme formation are not restricted to the erythropoietic system. Recent studies show that reduction of serum 1,25-dihydroxy vitamin D seen with even low level lead exposure is apparently the result of lead's inhibition of the activity of renal 1-hydroxylase, a cytochrome P-450 mediated enzyme. Cytochrome P-450, a heme-containing protein, is an integral part of the hepatic mixed function oxygenase system and is known to be affected in humans and animals by lead exposure, particularly acute intoxication. Reduced P-450 content has been found to be correlated with impaired activity of such detoxifying enzyme systems as aniline hydroxylase and aminopyrine demethylase.

Studies of organotypic chick dorsal root ganglion in culture show that the nervous system not only has heme biosynthetic capability but that such preparations elaborate porphyrinic material in the presence of lead. In the neonatal rat, chronic exposure to lead resulting in moderately elevated blood lead levels is associated with retarded growth in the hemoprotein cytochrome C and with disturbed electron transport in the developing rat cerebral cortex. These data parallel the effect of lead on ALA-D activity and ALA accumulation in neural tissue. When both of these effects are viewed within the toxicokinetic context of increased retention of lead in both developing animals and children, there is an obvious, serious potential for impaired heme-based metabolic function in the nervous system of lead-exposed children.

As can be seen from the above discussion, the health significance of ZPP accumulation rests with the fact that such build-up is evidence of impaired heme and hemoprotein formation in tissues, particularly the nervous system, arising from entry of lead into mitochondria. Such evidence for reduced heme synthesis is consistent with a diverse body of data documenting

lead-associated effects on mitochondria, including impairment of ferrochelatase activity. As a mitochondrial enzyme, ferrochelatase activity may be inhibited either directly by lead or indirectly by impairment of iron transport to the enzyme.

The relative value of the lead-ZPP relationship in erythropoietic tissue as an index of this effect in other tissues hinges on the relative sensitivity of the erythropoietic system compared with other systems. For example, one study of rats exposed to low levels of lead over their lifetime demonstrated that protoporphyrin accumulation in renal tissue was already significant at levels of lead exposure where little change was seen in erythrocyte porphyrin levels. The issue of sensitivity is obviously distinct from the question of which system is most accessible to measurement of the effect.

Other steps in the heme biosynthesis pathway are also known to be affected by lead, although these have not been studied as much on a biochemical or molecular level. Levels of coproporphyrin are increased in urine, reflecting active lead intoxication. Lead also affects the activity of the enzyme uroporphyrinogen-I-synthetase, resulting in an accumulation of its substrate, porphobilinogen. It has been reported that the erythrocyte enzyme is much more sensitive to lead than the hepatic species and presumably accounts for much of the accumulated substrate.

Anemia is a manifestation of chronic lead intoxication, being characterized as mildly hypochromic and usually normocytic. It is associated with reticulocytosis, owing to shortened cell survival, and the variable presence of basophilic stippling. Its occurrence is due to both decreased production and increased rate of destruction of erythrocytes. In children under four years of age, the anemia of iron deficiency is exacerbated by the effect of lead, and vice versa. Hemoglobin production is negatively correlated with blood lead in young children, where iron deficiency may be a confounding factor, as well as in lead workers. In one study, blood lead values that were usually below 80 µg/dl were inversely correlated with hemoglobin content. In these subjects, iron deficiency was found to be absent. The blood lead threshold for reduced hemoglobin content is about 50 µg/dl in adult lead workers and somewhat lower in children, around 40 µg/dl.

The mechanism of lead-associated anemia appears to be a combination of reduced hemoglobin production and shortened erythrocyte survival because of direct cell injury. Effects of lead on hemoglobin production involve disturbances of both heme and globin biosynthesis. The hemolytic component to lead-induced anemia appears to be due to increased cell fragility and increased osmotic resistance. In one study using rats, it was noted that the reduced cell deformability and consequent hemolysis associated with vitamin E deficiency is exacerbated by lead exposure. The molecular basis for increased cell destruction rests with inhibition of (Na^+, K^+)-ATPase and pyrimidine-5'-nucleotidase. Inhibition of the former enzyme leads to cell "shrinkage," and inhibition of the latter results in impaired pyrimidine nucleotide

phosphorolysis and disturbance of the activity of the purine nucleotides necessary for cellular energetics.

Tetraethyl lead and tetramethyl lead, components of leaded gasoline, undergo transformation *in vivo* to the neurotoxic trialkyl metabolites as well as further conversion to inorganic lead. Hence, one might anticipate that exposure to such agents may show effects commonly associated with inorganic lead in terms of heme synthesis and erythropoiesis.

Various surveys and case reports make it clear that the habit of sniffing leaded gasoline is associated with chronic lead intoxication in children from socially deprived backgrounds in rural or remote areas. Notable in these subjects is evidence of impaired heme biosynthesis as indexed by significantly reduced ALA-D activity. In a number of case reports of frank lead toxicity from habitual sniffing of leaded gasoline, such effects as basophilic stippling in erythrocytes and significantly reduced hemoglobin have also been noted.

Lead-associated disturbances of heme biosynthesis as a possible factor in the neurological effects of lead have been the object of considerable interest because of (1) the recognized similarity between the classical signs of lead neurotoxicity and a number of the neurological components of the congenital disorder known as acute intermittent porphyria, as well as (2) some of the unusual aspects of lead neurotoxicity. There are two possible points of connection between lead's effects on both heme biosynthesis and the nervous system. Concerning the similarity of lead neurotoxicity to acute intermittent porphyria, there is the common feature of excessive systemic accumulation and excretion of ALA. Second, lead neurotoxicity reflects, to some degree, impaired synthesis of heme and hemoproteins involved in crucial cellular functions. Available information indicates that ALA levels are elevated in the brain of lead-exposed animals, arising via *in situ* inhibition of brain ALA-D activity or via transport to the brain after formation in other tissues. ALA is known to traverse the blood-brain barrier. Hence, ALA is accessible to, or formed within, the brain during lead exposure and may express its neurotoxic potential.

Based on various *in vitro* and *in vivo* data obtained in the context of neurochemical studies of lead neurotoxicity, it appears that ALA can readily play a role in GABAergic function, particularly inhibiting release of the neurotransmitter GABA from presynaptic receptors, where ALA appears to be very potent even at low levels. In an *in vitro* study, agonist behavior by ALA was demonstrated at levels as low as 1.0 μM ALA. This *in vitro* observation supports results of a study using lead-exposed rats in which there was reported inhibition of both resting and K^+-stimulated preloaded ^3H-GABA. Further evidence for an effect of some agent other than lead acting directly is the observation that *in vivo* effects of lead on neurotransmitter function cannot be duplicated with *in vitro* preparations to which lead is added. Human data on lead-induced associations between disturbed heme synthesis and neurotoxicity, while limited, also suggest that ALA may function as a neurotoxicant.

The connection of impaired heme and hemoprotein synthesis in the brain of the neonatal rat was noted earlier. In these studies there was reduced cytochrome C production and impaired operation of the cytochrome C respiratory chain. Hence, one might expect that such impairment would be most prominent in areas of relatively greater cellularization, such as the hippocampus. As noted in Chapter 10, these are also regions where selective lead accumulation appears to occur.

1.12.4 Neurotoxic Effects of Lead

An assessment of the impact of lead on human and animal neurobehavioral function raises a number of issues. Among the key points addressed here are: (1) the internal exposure levels, as indexed by blood lead levels, at which various adverse neurobehavioral effects occur; (2) the reversibility of such deleterious effects; and (3) the populations that appear to be most susceptible to neural damage. In addition, the question arises as to the utility of using animal studies to draw parallels to the human condition.

1.12.4.1 Internal Lead Levels at which Neurotoxic Effects Occur. Markedly elevated blood lead levels are associated with the most serious neurotoxic effects of lead exposure (including severe, irreversible brain damage as indexed by the occurrence of acute or chronic encephalopathic symptoms, or both) in both humans and animals. For most human adults, such damage typically does not occur until blood lead levels exceed 120 μg/dl. Evidence does exist, however, for acute encephalopathy and death occurring in some human adults at blood lead levels of 100-120 μg/dl. In children, the effective blood lead level for producing encephalopathy or death is lower, starting at approximately 80-100 μg/dl. It should be emphasized that, once encephalopathy occurs, death is not an improbable outcome, regardless of the quality of medical treatment available at the time of acute crisis. In fact, certain diagnostic or treatment procedures themselves may exacerbate matters and push the outcome toward fatality if the nature and severity of the problem are not diagnosed or fully recognized. It is also crucial to note the rapidity with which acute encephalopathic symptoms can develop or death can occur in apparently asymptomatic individuals or in those apparently only mildly affected by elevated lead body burdens. Rapid deterioration often occurs, with convulsions or coma suddenly appearing with progression to death within 48 hours. This strongly suggests that even in apparently asymptomatic individuals, rather severe neural damage probably exists at high blood lead levels even though it is not yet overtly manifested in obvious encephalopathic symptoms. This conclusion is further supported by numerous studies showing that overtly lead intoxicated children with high blood lead levels, but not observed to manifest acute encephalopathic symptoms, are permanently cognitively impaired, as are most children who survive acute episodes of frank lead encephalopathy.

Recent studies show that overt signs and symptoms of neurotoxicity (indicative of both CNS and peripheral nerve dysfunction) are detectable in some human adults at blood lead levels as low as 40-60 μg/dl, levels well below the 60 or 80 μg/dl criteria previously discussed as being "safe" for adult lead exposures. In addition, certain electrophysiological studies of peripheral nerve function in lead workers, indicate that slowing of nerve conduction velocities in some peripheral nerves are associated with blood lead levels as low as 30-50 μg/dl (with no clear threshold for the effect being evident). These results are indicative of neurological dysfunctions occurring at relatively low lead levels in non-overtly lead intoxicated adults.

Other evidence tends to confirm that neural dysfunctions exist in apparently asymptomatic children, at similar or even lower levels of blood lead. The body of studies on low-or moderate-level lead effects on neurobehavioral functions in non-overtly lead intoxicated children, as evaluated in Chapter 12, presents an array of data pointing to that conclusion. Several well-controlled studies have found effects that are clearly statistically significant, whereas other have found nonsignificant but borderline effects. Some studies reporting generally nonsignificant findings at times contain data confirming some statistically significant effects, which the authors attribute to various extraneous factors. It should also be noted that, given the apparent nonspecific nature of some of the behavioral or neural effects probable at low levels of lead exposure, one would not expect to find striking differences in every instance. The lowest observed blood lead levels associated with significant neurobehavioral deficits indicative of CNS dysfunction, both in apparently asymptomatic children and in developing rats and monkeys generally appear to be in the range of 30-50 μg/dl. However, other types of neurotoxic effects, e.g., altered EEG patterns, have been reported at lower levels, supporting a continuous dose-response relationship between lead and neurotoxicity. Such effects, when combined with adverse social factors (such as low parental IQ, low socioeconomic status, poor nutrition, and poor quality of the caregiving environment) can place children, especially those below the age of three years, at significant risk. However, it must be acknowledged that nutritional covariates, as well as demographic social factors, have been poorly controlled in many of the human studies reviewed. Socioeconomic status also is a crude measure of parenting and family structure that requires further assessment as a possible contributor to observed results of neurobehavioral studies.

Timing, type, and duration of exposure are important factors in both animal and human studies. It is often uncertain whether observed blood lead levels represent the levels that were responsible for observed behavioral deficits or electrophysiological changes. Monitoring of lead exposures in human subjects in all cases has been highly intermittent or nonexistent during the period of life preceding neurobehavioral assessment. In most human studies, only

one or two blood lead values are provided per subject. Tooth lead may be an important cumulative exposure index, but its modest, highly variable correlation to blood lead or FEP and to external exposure levels makes findings from various studies difficult to compare quantitatively. The complexity of the many important covariates and their interaction with dependent variable measures of modest validity, e.g., IQ tests, may also account for some discrepancies among the different studies.

1.12.4.2 Early Development and the Susceptibility to Neural Damage. On the question of early childhood vulnerability, the neurobehavioral data are consistent with morphological and biochemical studies of the susceptibility of the heme biosynthetic pathway to perturbation by lead. Various lines of evidence suggest that the order of susceptibility to lead's effects is: (1) young > adults and (2) female > male. Animal studies also have pointed to the perinatal period of ontogeny as a particularly critical time for a variety of reasons: (1) it is a period of rapid development of the nervous system; (2) it is a period where good nutrition is particularly critical; and (3) it is a period where the caregiver environment is vital to normal development. However, the precise boundaries of a critical period are not yet clear and may vary depending on the species and function or endpoint that is being assessed. Nevertheless, there is general agreement that human infants and toddlers below the age of three years are at special risk because of in utero exposure, increased opportunity for exposure because of normal mouthing behavior, and increased rates of lead absorption due to various factors, e.g., nutritional deficiences.

1.12.4.3 The Question of Irreversibility. Little research on humans is available on persistence of effects. Some work suggests that mild forms of peripheral neuropathy in lead workers may be reversible after termination of lead exposure, but little is known regarding the reversibility of lead effects on central nervous system function in humans. A recent two-year follow-up study of 28 children of battery factory workers found a continuing relationship between blood lead levels and altered slow wave voltage of cortical slow wave potentials indicative of persisting CNS effects of lead. Current population studies, however, will have to be supplemented by prospective longitudinal studies of the effects of lead on development in order to address the issue of reversibility or persistence of lead neurotoxic effects in humans more satisfactorily.

Various animal studies provide evidence that alterations in neurobehavioral function may be long-lived, with such alterations being evident long after blood lead levels have returned to control levels. These persistent effects have been demonstrated in monkeys as well as rats under a variety of learning performance test paradigms. Such results are also consistent with morphological, electrophysiological, and biochemical studies on animals that suggest lasting changes in synaptogenesis, dendritic development, myelin and fiber tract formation, ionic mechanisms of neurotransmission, and energy metabolism.

1.12.4.4 Utility of Animal Studies in Drawing Parallels to the Human Condition. Animal models are used to shed light on questions where it is impractical or ethically unacceptable to use human subjects. This is particularly true in the case of exposure to environmental toxins such as lead. In the case of lead, it has been effective and convenient to expose developing animals via their mothers' milk or by gastric gavage, at least until weaning. In many studies, exposure was continued in the water or food for some time beyond weaning. This approach simulates at least two features commonly found in human exposure: oral intake and exposure during early development. The preweaning period in rats and mice is of particular relevance to in terms of parallels with the first two years or so of human brain development.

However, important questions exist concerning the comparability of animal models to humans. Given differences between humans, rats, and monkeys in heme chemistry, metabolism, and other aspects of physiology and anatomy, it is difficult to state what constitutes an equivalent internal exposure level (much less an equivalent external exposure level). For example, is a blood lead level of 30 μg/dl in a suckling rat equivalent to 30 μg/dl in a three-year-old child? Until an answer is available to this question, i.e., until the function describing the relationship of exposure indices in different species is available, the utility of animal models for deriving dose-response functions relevant to humans will be limited.

Questions also exist regarding the comparability of neurobehavioral effects in animals with human behavior and cognitive function. One difficulty in comparing behavioral endpoints such as locomotor activity is the lack of a consistent operational definition. In addition to the lack of standardized methodologies, behavior is notoriously difficult to "equate" or compare meaningfully across species because behavioral analogies do not demonstrate behavioral homologies. Thus, it is improper to assume, without knowing more about the responsible underlying neurological structures and processes, that a rat's performance on an operant conditioning schedule or a monkey's performance on a stimulus discrimination task corresponds to a child's performance on a cognitive function test. Still deficits in performance on such tasks are indicative of altered CNS function which is likely to parallel some type of altered human CNS function as well.

In terms of morphological findings, there are reports of hippocampal lesions in both lead-exposed rats and humans that are consistent with a number of behavioral findings suggesting an impaired ability to respond appropriately to altered contingencies for rewards. That is, subjects tend to persist in certain patterns of behavior even when changed conditions make the behavior inappropriate. Other morphological findings in animals, such as demyelination and glial cell decline, are comparable to human neuropathologic observations mainly at relatively high exposure levels.

Another neurobehavioral endpoint of interest in comparing human and animal neurotoxicity of lead is electrophysiological function. Alterations of electroencephalographic patterns and

cortical slow wave voltage have been reported for lead-exposed children, and various electrophysiological alterations both in vivo (e.g., in rat visual evoked response) and in vitro (e.g., in frog miniature endplate potentials) have also been noted in laboratory animals. At this time, however, these lines of work have not converged sufficiently to allow for strong conclusions regarding the electrophysiological aspects of lead neurotoxicity.

Biochemical approaches to the experimental study of leads effects on the nervous system have generally been limited to laboratory animal subjects. Although their linkage to human neurobehavioral function is at this point somewhat speculative, such studies do provide insight to possible neurochemical intermediaries of lead neurotoxicity. No single neurotransmitter system has been shown to be particularly sensitive to the effects of lead exposure; rather, lead-induced alterations have been demonstrated in several different neurotransmitter systems, including dopamine, norepinephrine, serotonin, and gamma-aminobutyric acid. In addition, lead has been shown to have subcellular effects in the central nervous system at the level of mitochondrial function and protein synthesis.

Given the above-noted difficulties in formulating a comparative basis for internal exposure levels among different species, the primary value of many animal studies, particularly in vitro studies, may be in the information they can provide on basic mechanisms involved in lead neurotoxicity. A number of in vitro studies show that significant, potentially deleterious effects on nervous system function occur at in situ lead concentrations of 5 μM and possibly lower, suggesting that no threshold may exist for certain neurochemical effects of lead on a subcellular or molecular level. The relationship between blood lead levels and lead concentrations at such extra- or intracellular sites of action, however, remains to be determined. Despite the problems in generalizing from animals to humans, both the animal and the human studies show great internal consistency in that they support a continuous dose-response functional relationship between lead and neurotoxic biochemical, morphological, electrophysiological, and behavioral effects.

1.12.5 Effects of Lead on the Kidney

It has been known for more than a century that kidney disease can result from lead poisoning. Identifying the contributing causes and mechanisms of lead-induced nephropathy has been difficult, however, in part because of the complexities of human exposure to lead and other nephrotoxic agents.

Nevertheless, it is possible to estimate at least roughly lead exposure ranges associated with detectable renal dysfunction in both human adults and children. More specifically, numerous studies of occupationally exposed workers have provided evidence for lead-induced chronic nephropathy being associated with blood lead levels ranging from 40 to more than

100 µg/dl, and some are suggestive of renal effects possibly occurring even at levels as low as 30 µg/dl. Similarly, in children, the relatively sparse evidence available points to the manifestation of renal dysfunction, as indexed for example by generalized aminoaciduria, at blood lead levels across the range of 40 to more than 100 µg/dl. The current lack of evidence for renal dysfunction at lower blood lead levels in children may simply reflect the greater clinical concern with neurotoxic effects of lead intoxication in children. The persistence of lead-induced renal dysfunction in children also remains to be more fully investigated, although a few studies indicate that children diagnosed as being acutely lead poisoned experience lead nephropathy effects lasting throughout adulthood.

Parallel results from experimental animal studies reinforce the findings in humans and help illuminate the mechanisms underlying such effects. For example, a number of transient effects in human and animal renal function are consistent with experimental findings of reversible lesions such as nuclear inclusion bodies, cytomegaly, swollen mitochondria, and increased numbers of iron-containing lysosomes in proximal tubule cells. Irreversible lesions such as interstitial fibrosis are also well documented in both humans and animals following chronic exposure to high doses of lead. Functional renal changes observed in humans have also been confirmed in animal model systems with respect to increased excretion of amino acids and elevated serum urea nitrogen and uric acid concentrations. The inhibitory effects of lead exposure on renal blood flow and glomerular filtration rate are currently less clear in experimental model systems; further research is needed to clarify the effects of lead on these functional parameters in animals. Similarly, while lead-induced perturbation of the renin-angiotensin system has been demonstrated in experimental animal models, further research is needed to clarify the exact relationships among lead exposure (particularly chronic low-level exposure), alteration of the renin-angiotensin system, and hypertension in both humans and animals.

On the biochemical level, it appears that lead exposure produces changes at a number of sites. Inhibition of membrane marker enzymes, decreased mitochondrial respiratory function/cellular energy production, inhibition of renal heme biosynthesis, and altered nucleic acid synthesis are the most marked changes to have been reported. The extent to which these mitochondrial alterations occur is probably mediated in part by the intracellular bioavailability of lead, which is determined by its binding to high affinity kidney cytosolic binding proteins and deposition within intranuclear inclusion bodies.

Recent studies in humans have indicated that the EDTA lead-mobilization test is the most reliable technique for detecting persons at risk for chronic nephropathy. Blood lead measurements are a less satisfactory indicator because they may not accurately reflect cumulative absorption some time after exposure to lead has terminated.

A number of major questions remain to be more definitively answered concerning the effect of lead on the kidney. Can a distinctive lead-induced renal lesion be identified either in functional or histologic terms? What biologic measurements are most reliable for the prediction of lead-induced nephropathy? What is the incidence of lead nephropathy in the general population as well as among specifically defined subgroups with varying exposure? What is the natural history of treated and untreated lead nephropathy? What is the mechanism of lead-induced hypertension and renal injury? What are the contributions of environmental and genetic factors to the appearance of renal injury due to lead? At what level of lead in blood can the kidneys be affected? Is there a threshold for renal effects of lead? The most difficult question to answer may well be to determine the contribution of low levels of lead exposure to renal disease of non-lead etiologies.

1.12.6 Effects of Lead on Reproduction and Development

Data from human and animal studies indicate that lead may exert gametotoxic, embryotoxic, and (according to some animal studies) teratogenic effects that may influence the survival and development of the fetus and newborn. Prenatal viability and development, it appears, may also be affected indirectly, contributing to concern for unborn children and, therefore, pregnant women or childbearing-age women being groups at special risk for lead effects. Early studies of quite high dose lead exposure in pregnant women indicate toxic--but not teratogenic--effects on the conceptus. Effects on reproductive performance in women at lower exposure levels are not well documented. Unfortunately, currently available human data regarding lead effects on the fetus during development generally do not lend themselves to accurate estimation of lowest observed or no-effect levels. However, some studies have shown that fetal heme synthesis is affected at maternal and fetal blood lead levels as low as approximately 15 µg/dl, as indicated by urinary ALA levels and ALA-D activity. This observed effect level is consistant with lowest observed effect levels for indications of altered heme synthesis seen at later ages for preschool and older children.

There are currently no reliable data pointing to adverse effects in human offspring following paternal exposure to lead, but industrial exposure of men to lead at levels resulting in blood lead values of 40-50 µg/dl appear to have resulted in altered testicular function. Also, another study provided evidence of effects on prostatic and seminal vesicle functions at 40-50 µg/dl blood lead levels in lead workers.

The paucity of human exposure data force an examination of the animal studies for indications of threshold levels for effects of lead on the conceptus. It must be noted that the animal data are almost entirely derived from rodents. Based on these rodent data, it seems likely that fetotoxic effects have occurred in animals at chronic exposures to 600-1000 ppm

lead in the diet. Subtle effects on fetal physiology and metabolism appear to have been observed in rats after chronic maternal exposure to 10 ppm lead in drinking water, while similar effects of inhaled lead have been seen at chronic levels of 10 $\mu g/m^3$. With acute exposure by gavage or by injection, the values are 10-16 mg/kg and 16-30 mg/kg, respectively. Since humans are most likely to be exposed to lead in their diet, air, or water, the data from other routes of exposure are of less value in estimating harmful exposures. Indeed, it seems likely that teratogenic effects occur only when the maternal dose is given by injection.

Although human and animal responses may be dissimilar, the animal evidence does document a variety of effects of lead exposure on reproduction and development. Measured or apparent changes in production of or response to reproductive hormones, toxic effects on the gonads, and toxic or teratogenic effects on the conceptus have all been reported. The animal data also suggest subtle effects on such parameters as metabolism and cell structure that should be monitored in human populations. Well designed human epidemiological studies involving large numbers of subjects are still needed. Such data could clarify the relationship of exposure levels and durations to blood lead values associated with significant effects, and are needed for estimation of no-effect levels.

Given that the most clear-cut data concerning the effects of lead on reproduction and development are derived from studies employing high lead doses in laboratory animals, there is still a need for more critical research to evaluate the possible subtle toxic effects of lead on the fetus, using biochemical, ultrastructural, or neurobehavioral endpoints. An exhaustive evaluation of lead-associated changes in offspring will require consideration of possible additional effects due to paternal lead burden. Neonatal lead intake via consumption of milk from lead-exposed mothers may also be a factor at times. Also, it must be recognized that lead effects on reproduction may be exacerbated by other environmental factors (e.g., dietary influences, maternal hyperthermia, hypoxia, and co-exposure to other toxins).

1.12.7. Genotoxic and Carcinogenic Effects of Lead

It is difficult to conclude what role lead may play in the induction of human neoplasia. Epidemiological studies of lead-exposed workers provide no definitive findings. However, statistically significant elevations in cancer of the respiratory tract and digestive system in workers exposed to lead and other agents warrant some concern. Since it is clear that lead acetate can produce renal tumors in some experimental animals, it seems reasonable to conclude that at least that particular lead compound should be regarded as a carcinogen and prudent to treat it as if it were also human carcinogen (as per IARC conclusions and recommendations). However, this statement is qualified by noting that lead has been seen to increase tumorogenesis rates in animals only at relatively high concentrations, and therefore does not seem to be an extremely potent carcinogen. *In vitro* studies further support the genotoxic and carcinogenic role of lead, but also indicate that lead is not extremely potent in these systems.

1.12.8. Effects of Lead on the Immune System

Lead renders animals highly susceptible to endotoxins and infectious agents. Host susceptibility and the humoral immune system appear to be particularly sensitive. As postulated in recent studies, the macrophage may be the primary immune target cell of lead. Lead-induced immunosuppression occurs at low lead exposures (blood lead levels in the 20-40 μg/dl range) that, although they induce no overt toxicity, may nevertheless be detrimental to health. Available data provide good evidence that lead affects immunity, but additional studies are necessary to elucidate the actual mechanisms by which lead exerts its immunosuppressive action. Knowledge of lead effects on the human immune system is lacking and must be ascertained in order to determine permissible levels for human exposure. However, in view of the fact that lead affects immunity in laboratory animals and is immunosuppressive at very low dosages, its potential for serious effects in humans should be carefully considered.

1.12.9 Effects of Lead on Other Organ Systems

The cardiovascular, hepatic, endocrine, and gastrointestional systems generally show signs of dysfunction mainly at relatively high lead exposure levels. Consequently, in most clinical and experimental studies attention has been primarily focused on more sensitive and vulnerable target organs, such as the hematopoietic and nervous systems. However, it should be noted that overt gastrointestinal symptoms associated with lead intoxication have been observed in some recent studies to occur in lead workers at blood lead levels as low as 40-60 μg/dl, suggesting that effects on the gastrointestinal and the other above organ systems may occur at relatively low exposure levels but remain to be demonstrated by future scientific investigations.

1.13 EVALUATION OF HUMAN HEALTH RISKS ASSOCIATED WITH EXPOSURE TO LEAD AND ITS COMPOUNDS

1.13.1 Introduction

This section attempts to integrate, concisely, key information and conclusions discussed in preceding sections into a coherent framework by which interpretation and judgments can be made concerning the risk to human health posed by present levels of lead contamination in the United States.

In regard to various health effects of lead, the main emphasis here is on the identification of those effects most relevant to various segments of the general U.S. population and the placement of such effects in a dose-effect/dose-response framework. In regard to the latter, a crucial issue has to do with relative response of various segments of the population in terms of effect thresholds as indexed by some exposure indicator. Furthermore, it is of interest to assess the extent to which available information supports the notion of a continuum of effects as one proceeds across the spectrum of exposure levels. Finally, it is of

interest to ascertain the availability of data on the relative number or percentage of members (i.e., "responders") of specific population groups that can be expected to experience a particular effect at various lead exposure levels in order to permit delineation of dose-response curves for the relevant effects in different segments of the population. These matters are discussed in Sections 1.13.5 and 1.13.6.

Melding of information from the sections on lead exposure, metabolism, and biological effects permits the identification of population segments at special risk in terms of physiological and other host characteristics, as well as heightened vulnerability to a given effect; and these risk groups are discussed in Section 1.13.7. With demographic identification of individuals at risk, one may then draw upon population data from other sources to obtain a numerical picture of the magnitude of population groups at potential risk. This is also discussed in Section 1.13.7.

1.13.2 EXPOSURE ASPECTS

1.13.2.1 Levels of Lead in Various Media of Relevance to Human Exposure

Human populations in the United States are exposed to lead in air, food, water, and dust. In rural areas, Americans not occupationally exposed to lead consume 50 to 75 μg Pb/day. This level of exposure is referred to as the baseline exposure because it is unavoidable except by drastic change in lifestyle or by regulation of lead in foods or ambient air. There are several environmental circumstances that can increase human exposures above baseline levels. Most of these circumstances involve the accumulation of atmospheric dusts in the work and play environments. A few, such as pica and family home gardening, may involve consumption of lead from chips of exterior or interior house paint.

Ambient Air Lead Levels. Monitored ambient air lead concentration values in the U.S. are contained in two principal data bases: (1) EPA's National Air Sampling Network (NASN), recently renamed National Filter Analysis Network (NFAN); and (2) EPA's National Aerometric Data Bank, consistting of measurements by state and local agencies in conjunction with compliance monitoring for the current ambient air lead standard.

NASN data for 1982, the most current year in the annual surveys, indicate that most of the urban sites show reported annual averages below 0.7 μg Pb/m^3, while the majority of the non-urban locations have annual figures below 0.2 μg Pb/m^3. Over the interval 1976-1981, there has been a downward trend in these averages, mainly attributable to decreasing lead content of leaded gasoline and the increasing usage of lead-free gasoline. Furthermore, examination of quarterly averages over this interval shows a typical seasonal variation, characterized by maximum air lead values in winter and minimum values in summer.

With respect to the particle size distribution of ambient air lead, EPA studies using cascade impactors in six U.S. cities have indicated that 60 to 75 percent of such air lead was

associated with sub-micron particles. This size distribution is significant in considering the distance particles may be transported and the deposition of particles in the pulmonary compartment of the respiratory tract. The relationship between airborne lead at the monitoring station and the lead inhaled by humans is complicated by such variables as vertical gradients, relative positions of the source, monitor, and the person, and the ratio of indoor to outdoor lead concentrations. To obtain an accurate picture of the amount of lead inhaled during the normal activities of an individual, personal monitors would probably be the most effective. But the information gained would be insignificant, considering that inhaled lead is only a small fraction of the total lead exposure, compared to the lead in food, beverages, and dust. The critical question with respect to airborne lead is how much lead becomes entrained in dust. In this respect, the existing monitoring network may provide an adequate estimate of the air concentration from which the rate of deposition can be determined. The percentage of ambient air lead which represents alkyl forms was noted in one study to range from 0.3 to 2.7 percent, rising up to about 10 percent at service stations.

Levels of Lead In Dust. The lead content of dusts can figure prominently in the total lead exposure picture for young children. Lead in aerosol particles deposited on rigid surfaces in urban areas (such as sidewalks, porches, steps, parking lots, etc.) does not undergo dilution compared to lead transferred by deposition onto soils. Dust can approach extremely high concentrations. Dust lead can accumulate in the interiors of dwellings as well as in the outside surroundings, particularly in urban areas.

Measurements of soil lead to a depth of 5 cm in areas of the U.S., using sites near roadways, were shown in one study to range from 150 to 500 µg Pb/g dry weight close to roadways (i.e., within 8 meters). By contrast, lead in dusts deposited on or near heavily traveled traffic arteries show levels in major U.S. cities ranging up to 8000 µg Pb/g and higher. In residential areas, exterior dust lead levels are 1000 µg/g or less. Levels of lead in house dust can be significantly elevated. A study of house dust samples in Boston and New York City revealed levels of 1000 to 2000 µg Pb/g. Some soils adjacent to houses with exterior lead-based paints may have lead concentrations greater than 10,000 µg/g.

Thirty-four percent of the baseline consumption of lead by children comes from the consumption of 0.1 g of dust per day (Tables 1-13 and 1-14). Ninety percent of this dust lead is of atmospheric origin. Dust also accounts for more than ninety percent of the additive lead attributable to residences in an urban environment or near a smelter (Table 1-15).

Levels of Lead in Food. The route by which adults and older children in the baseline population of the U.S. receive the largest proportion of lead intake is through foods, with reported estimates of the dietary lead intake for Americans ranging from 60 to 75 µg/day. The added exposure from living in an urban environment is about 30 µg/day for adults and 100 µg/day for children, all of which can be attributed to atmospheric lead.

TABLE 1-13. SUMMARY OF BASELINE HUMAN EXPOSURES TO LEAD†

Source	Total Lead Consumed	Percent of Total Consumption	Soil		Direct Atmospheric Lead*	Lead from Solder or Other Metals	Lead of Undetermined Origin
			Natural Lead Consumed	Indirect Atmospheric Lead*			
Child 2-yr old							
Inhaled Air	0.5	0.8%	0.001	-	0.5	-	-
Food	28.7	46.7	0.9	0.9	10.9	10.3	17.6
Water & beverages	11.2	18.3	0.01	2.1	1.2	7.8	-
Dust	21.0	34.2	0.6	-	19.0	-	1.4
Total	61.4		1.5	3.0	31.6	18.1	19.0
Percent	100%		2.4%	4.9%	51.5%	29.5%	22.6%
Adult female							
Inhaled Air	1.0	1.8%	0.002	-	1.0	-	-
Food	33.2	58.7	1.0	1.0	12.6	11.9	21.6
Water & beverages	17.9	31.6	0.01	3.4	2.0	12.5	-
Dust	4.5	7.9	0.2	-	2.9	-	1.4
Total	56.6		1.2	4.4	18.5	24.4	23.0
Percent	100%		2.1%	7.8%	32.7%	43.1%	26.8%
Adult male							
Inahaled air	1.0	1.3%	0.002	-	1.0	-	-
Food	45.7	59.9	1.4	1.4	17.4	16.4	31.5
Water & beverages	25.1	32.9	0.1	4.7	2.8	17.5	-
Dust	4.5	5.9	0.2	-	2.9	-	1.4
Total	76.3		1.7	6.1	24.1	33.9	32.9
Percent	100%		2.2%	8.0%	31.6%	44.4%	27.1%

*Indirect atmospheric lead has been previously incorporated into soil, and will probably remain in the soil for decades or longer. Direct atmospheric lead has been deposited on the surfaces of vegetation and living areas or incorporated during food processing shortly before human consumption. It may be assumed that 85 percent of direct atmospheric lead derives from gasoline additives.

†units are in µg/day.

TABLE 1-14. RELATIVE BASELINE HUMAN LEAD EXPOSURES EXPRESSED PER KILOGRAM BODY WEIGHT*

	Total Lead Consumed	Total Lead Consumed Per Kg Body Wt µg/Kg·Day	Atmospheric Lead Per Kg Body Wt µg/Kg·Day
Child (2 yr old)	(µg/day)		
Inhaled air	0.5	0.05	0.05
Food	28.7	2.9	1.1
Water and beverages	11.2	1.1	0.12
Dust	21.0	2.1	1.9
Total	61.4	6.15	3.17
Adult female			
Inhaled air	1.0	0.02	0.02
Food	33.2	0.66	0.25
Water and beverages	17.9	0.34	0.04
Dust	4.5	0.09	0.06
Total	56.6	1.13	0.37
Adult male			
Inhaled air	1.0	0.014	0.014
Food	45.7	0.65	0.25
Water and beverages	25.1	0.36	0.04
Dust	4.5	0.064	0.04
Total	76.3	1.088	0.344

*Body weights: 2 year old child = 10/kg; adult female = 50 kg; adult male = 70 kg.

Atmospheric lead may be added to food crops in the field or pasture, during transportation to the market, during processing, and during kitchen preparation. Metallic lead, mainly solder, may be added during processing and packaging. Other sources of lead, as yet undetermined, increase the lead content of food between the field and dinner table. American children, adult females, and adult males consume 29, 33 and 46 µg Pb/day, respectively, in milk and nonbeverage foods. Of these amounts, 38 percent is of direct atmospheric origin, 36 percent is of metallic origin and 20 percent is of undetermined origin.

Processing of foods, particularly canning, can significantly add to their background lead content, although it appears that the impact of this is being lessened with the trend away from use of lead-soldered cans. The canning process can increase lead levels 8-to 10-fold higher than for the corresponding uncanned food items. Home food preparation can also be a source of additional lead in cases where food preparation surfaces are exposed to moderate amounts of high-lead household dust.

TABLE 1-15. SUMMARY OF POTENTIAL ADDITIVE EXPOSURES TO LEAD

	Total Lead Consumed (µg/day)	Atmospheric Lead Consumed (µg/day)	Other Lead Sources (µg/day)
Baseline exposure:			
Child (2 yr old)			
Inhaled air	0.5	0.5	-
Food, water & beverages	39.9	12.1	27.8
Dust	21.0	19.0	2.0
Total baseline	61.4	31.6	29.8
Additional exposure due to:			
urban atmospheres:[1]			
air inhalation	7	7	0
dust	72	71	1
family gardens[2]	800	200	600
interior lead paint[3]	85	-	85
residence near smelter:[4]			
air inhalation	60	60	-
dust	2250	2250	-
secondary occupational[5]	150	-	-
Baseline exposure:			
Adult Male			
Inhaled air	1.0	1.0	-
Food, water & beverages	70.8	20.2	50.6
Dust	4.5	2.9	1.6
Total baseline	76.3	24.1	52.2
Additional exposure due to:			
urban atmospheres:[1]			
air inhalation	14	14	-
dust	7	7	-
family gardens[2]	2000	500	1500
interior lead paint[3]	17	-	17
residence near smelter:[4]			
air inhalation	120	120	-
dust	250	250	-
occupational[6]	1100	1100	-
secondary occupational[5]	21	-	-
smoking	30	27	3
wine consumption	100	?	?

[1]includes lead from household and street dust (1000 µg/g) and inhaled air (.75 µg/m³)

[2]assumes soil lead concentration of 2000 µg/g; all fresh leafy and root vegetables, sweet corn of Table 7-15 replaced by produce from garden. Also assumes 25% of soil lead is of atmospheric origin.

[3]assumes household dust rises from 300 to 2000 µg/g. Dust consumption remains the same as baseline. Does not include consumption of paint chips.

[4]assumes household and street dust increases to 25,000 µg/g, inhaled air increases to 6 µg/m³.

[5]assumes household dust increases to 2400 µg/g.

[6]assumes 8 hr shift at 16 µg Pb/m³ or 90% efficiency of respirators at 100 µg/ Pb/m³. and occupational dusts at 100,000 µg/m³.

Lead Levels in Drinking Water. Lead in drinking water may result from contamination of the water source or from the use of lead materials in the water distribution system. Lead entry into drinking water from the latter is increased in water supplies which are plumbo-solvent, i.e., with a pH below 6.5. Exposure of individuals occurs through direct ingestion of the water or via food preparation in such water.

The interim EPA drinking water standard for lead is 0.05 μg/g (50 μg/l) and several extensive surveys of public water supplies indicate that only a limited number of samples exceeded this standard on a nationwide basis. For example, a survey of interstate carrier water supplies conducted by EPA showed that only 0.3 percent exceeded the standard.

The major source of lead contamination of drinking water is the distribution system itself, particularly in older urban areas. Highest levels are encountered in "first-draw" samples, i.e., water sitting in the piping system for an extended period of time. In a large community water supply survey of 969 systems carried out in 1969-1970, it was found that the prevalence of samples exceeding 0.05 μg/g was greater where water was plumbo-solvent.

Most drinking water, and the beverages produced from drinking water, contain 0.008 to 0.02 μg Pb/g. The exceptions are canned juices and soda pop, which range from 0.033 to 0.052 μg/g. About 11 percent of the lead consumed in drinking water and beverages is of direct atmospheric origin, 70 percent comes from solder and other metals.

Lead in Other Media. Flaking lead paint in deteriorated housing stock in urban areas of the Northeast and Midwest has long been recognized as a major source of lead exposure for young children residing in this housing stock, particularly for children with pica. Individuals who are cigarette smokers may inhale significant amounts of lead in tobacco smoke. One study has indicated that the smoking of 30 cigarettes daily results in lead intake equivalent to that of inhaling lead in ambient air at a level of 1.0 μg Pb/m^3.

Cumulative Human Lead Intake From Various Sources. Table 1-13 shows the baseline of human lead exposures as described in detail in Chapter 7. These data show that atmospheric lead accounts for at least 30 percent of the baseline adult consumption and 50 percent of the daily consumption by a 2 yr old child. These percentages are conservative estimates because a part of the lead of undetermined origin may originate from atmospheric lead not yet accounted for.

From Table 1-14, it can be seen that young children have a dietary lead intake rate, that is 5-fold greater than for adults, on a body weight basis. To these observations must be added that absorption rates for lead are higher in children than in adults by at least 3-fold. Overall, then, the rate of lead entry into the blood stream of children, on a body weight basis, is estimated to be twice that of adults from the respiratory tract and 6 and 9 times greater from the GI tract. Since children consume more dust than adults, the atmospheric fraction of the baseline exposure is ten-fold higher for children than for adults, on a body

weight basis. These differences generally tend to place young children at greater risk, in terms of relative amounts of proportions of atmospheric lead absorbed per kg body weight, than adults under any given lead exposure situation.

1.13.3 LEAD METABOLISM: KEY ISSUES FOR HUMAN HEALTH RISK EVALUATION

From the detailed discussion of those various quantifiable characteristics of lead toxicokinetics in humans and animals presented in Chapter 10, several clear issues emerge as being important for full evaluation of the human health risk posed by lead:

(1) Differences in systemic or internal lead exposure of groups within the general population in terms of such factors as age/development and nutritional status; and

(2) The relationship of indices of internal lead exposures to both environmental levels of lead and tissues levels/effects.

Item 1 provides the basis for identifying segments within human populations at increased risk in terms of exposure criteria and is used along with additional information on relative sensitivity to lead health effects for identification of risk populations. The chief concern with item 2 is the adequacy of current means for assessing internal lead exposure in terms of providing adequate margins of protection from lead exposures producing health effects of concern.

1.13.3.1 Differential Internal Lead Exposure Within Population Groups

Compared to adults, young children take in more lead through the gastrointestinal and respiratory tracts on a unit body weight basis, absorb a greater fraction of this lead intake, and also retain a greater proportion of the absorbed amount.

Unfortunately, such amplification of these basic toxicokinetic parameters in children vs. adults also occurs at the time when: (1) humans are developmentally more vulnerable to the effects of toxicants such as lead in terms of metabolic activity, and (2) the interactive relationships of lead with such factors as nutritive elements are such as to induce a negative course toward further exposure risk.

Typical of physiological differences in children vs. adults in terms of lead exposure implications is a more metabolically active skeletal system in children. In children, turnover rates of bone elements such as calcium and phosphorus are greater than in adults, with correspondingly greater mobility of bone-sequestered lead. This activity is a factor in the observation that the skeletal system of children is relatively less effective as a depository for lead than in adults.

Metabolic demand for nutrients, particularly calcium, iron, phosphorus, and the trace nutrients, is such that widespread deficiencies of these nutrients exist, particularly among poor children. The interactive relationships of these elements with lead are such that defi-

ciency states both enhance lead absorption/retention and, as in the case of lead-induced reductions in 1,25-dihydroxyvitamin D, establish increasingly adverse interactive cycles.

Quite apart from the physiological differences which enhance internal lead exposure in children is the unique relationship of 2- to 3-year-olds to their exposure setting by way of normal mouthing behavior and the extreme manifestation of this behavior, pica. This behavior occurs in the same age group which studies have consistently identified as having a peak in blood lead. A number of investigations have addressed the quantification of this particular route of lead exposure, and it is by now clear that such exposure will dominate other routes when the child's surroundings, e.g., dust and soil, are significantly contaminated by lead.

Information provided in Chapter 10 also makes it clear that lead traverses the human placental barrier, with lead uptake by the fetus occurring throughout gestation. Such uptake of lead poses a potential threat to the fetus via an impact on the embryological developement of the central nervous and other systems. Hence, the only logical means of protecting the fetus from lead exposure is exposure control during pregnancy.

Within the general population, then, young children and pregnant women qualify as definale risk groups for lead exposure. Occupational exposure to lead, particularly among lead workers, logically defines these individuals as being in a high-risk category; work place contact is augmented by those same routes and levels of lead exposure affecting the rest of the adult population. From a biological point of view, lead workers do not differ from the general adult population with respect to the various toxicokinetic parameters and any differences in exposure control--occupational vs. non-occupational populations--as they exist are based on factors other than toxicokinetics.

1.13.3.2 Indices of Internal Lead Exposure and Their Relationship To External Lead Levels and Tissue Burdens/Effects

Several points are of importance in this area of lead toxicokinetics. They are: (1) the temporal characteristics of indices of lead exposure; (2) the relationship of the indicators to external lead levels; (3) the validity of indicators of exposure in reflecting target tissue burdens; (4) the interplay between these indicators and lead in body compartments; and (5) those various aspects of the issue with particular reference to children.

At this time, blood lead is widely held to be the most convenient, if imperfect, index of both lead exposure and relative risk for various adverse health effects. In terms of exposure, however, it is generally accepted that blood lead is a temporally variable measure which yields an index of relatively recent exposure because of the rather rapid clearance of absorbed lead from the blood. Such a measure, then, is of limited usefulness in cases where exposure is variable or intermittent over time, as is often the case with pediatric lead exposure.

Mineralizing tissue, specifically deciduous teeth, accumulate lead over time in proportion to the degree of lead exposure, and analysis of this material provides an assessment integrated over a greater time period and of more value in detecting early childhood exposure.

These two methods of assessing internal lead exposure have obvious shortcomings. A blood lead value will say little about any excessive lead intake at early periods, even though such remote exposure may have resulted in significant injury. On the other hand, whole tooth or dentine analysis is retrospective in nature and can only be done after the particularly vulnerable age in children under 4 to 5 years-- has passed. Such a measure, then provides little utility upon which to implement regulatory policy or clinical intervention.

The dilemmas posed by these existing methods may be able to be resolved by in situ analysis of teeth and bone lead, such that the intrinsic advantage of mineral tissue as a cumulative index is combined with measurement which is temporally concordant with on-going exposure. Work in several laboratories offers promise for such in situ analysis (See Chapters 9 and 10).

A second issue concerning internal indices of exposure and environmental lead is the relationship of changes in lead content of some medium with changes in blood content. Much of Chapter 11 was given over to description of the mathematical relationships of blood lead with lead in some external medium-- air, food, water, etc., without consideration of the biological underpinnings for these relationships.

Over a relatively broad range of lead exposure through some medium, the relationship of lead in the external medium to blood lead is curvilinear, such that relative change in blood lead per unit change in medium level generally becomes increasingly less as exposure increases. This behavior may reflect changes in tissue lead kinetics, reduced lead absorption, or increased excretion. Limited animal data would suggest that changes in excretion or absorption are not factors in this phenomenon. In any event, modest changes in blood levels with exposure at the higher end of this range are in no way to be taken as reflecting concomitantly modest changes in body or tissue lead uptake. Evidence continues to accumulate which suggests that an indicator such as blood lead is an imperfect measure of tissue lead burdens and of changes in such tissue levels in relation to changes in external exposure.

In Chapter 10, it was pointed out that blood lead is logarithmically related to chelatable lead (the latter being a more useful measure of the potentially toxic fraction of body lead), such that a unit change in blood lead is associated with an increasingly larger amount of chelatable lead. One consequence of this relationship is that moderately elevated blood lead values will tend to mask the "margin of safety" in terms of mobile body lead burdens. Such masking is apparent in one study of children where chelatable lead levels in children showing moderate elevations in blood lead overlapped those obtained in subjects showing frank plumbism, i.e. overt lead intoxication.

Related to the above is the question of the source of chelatable lead. It was noted in Chapter 10 that some sizable fraction of chelatable lead is derived from bone and this compels reappraisal of the notion that bone is an "inert sink" for otherwise toxic body lead. The notion of bone lead as toxicologically inert never did accord with what was known from studies of bone physiology, i.e., that bone is a "living" organ, and the thrust of recent studies of chelatable lead (as well as interrelationships of lead and bone metabolism) is toward bone lead being viewed as actually an insidious source of long-term systemic lead exposure rather than a protective mechanism permitting significant lead contact in industrialized populations.

The complex interrelationships of lead exposure, blood lead, and lead in body compartments is of particular interest in considering the disposition of lead in young children. Since children take in more lead on a weight basis, and absorb and retain more of this lead than the adult, one might expect that either tissue and blood levels would be significantly elevated or that the child's skeletal system would be more efficient in lead sequestration.

Blood lead levels in young children are either similar to adults (males) or somewhat higher (adult females). Limited autopsy data, furthermore, indicate that soft tissue levels in children are not markedly different from adults, whereas the skeletal system shows an approximate 2-fold increase in lead concentration from infancy to adolescence. Neglected in this observation is the fact that the skeletal system in children grows at an exponential rate, so that skeletal mass increases 40-fold during the interval in childhood when bone lead levels increase 2-fold, resulting in an actual increase of approximately 80-fold in total skeletal lead. If the skeletal growth factor is taken into account, along with growth in soft tissue and the expansion of vascular fluid volumes, the question of lead disposition in children is better understood.

Finally, limited animal data indicate that blood lead alterations with changes in lead exposure are poor indicators of such changes in target tissue. Specifically, it appears that abrupt reduction of lead exposure will be more rapidly reflected in blood lead than in such target tissues as the central nervous system, especially in the developing organism. This discordance may underlie the observation that severe lead neurotoxicity in children is associated with a rather broad range of blood lead values (see Section 1.12.4).

The above discussion of some of the problems with the use of blood lead in assessing target tissue burdens or the toxicologically active fraction of total body lead highlights the the inherent toxicokinetic problems with use of blood lead levels in defining margins of safety for avoiding internal lead exposure levels associated with undue risk of adverse effects. If, for example, blood lead levels of 40-50 μg/dl in "asymptomatic" children are associated with chelatable lead burdens which overlap those encountered in frank pediatric plumbism, as documented in one series of lead-exposed children, then there is no margin of safety at these blood levels for severe effects which are not at all a matter of controversy. Were it both

logistically feasible to do so on a large scale and were the use of chelants free of health risk to the subjects, serial provocative chelation testing would appear to be the better indicator of exposure and risk. Failing this, the only prudent alternative is the use of a large safety factor applied to blood lead which would translate to an "acceptable" chelatable burden. It is likely that this blood lead value would lie well below the currently accepted upper limit of 30 µg/dl, since the safety factor would have to be large enough to protect against frank plumbism as well as more subtle health effects seen with non-overt lead intoxication. This rationale from the standpoint of lead toxicokinetics is in accord also with the growing data base for dose-effect relationships of lead's effects on heme biosynthesis, erythropoiesis, and the nervous system in humans as summarized in Sections 1.12.3 and 1.12.4.

The future developement and routine use of in situ mineral tissue testing at time points concordant with on-going exposure and the comparison of such results with simultaneous blood lead and chelatable lead measurement would be of significant value in further defining what level of blood lead is indeed an acceptable upper limit.

1.13.3.3 Proportional Contributions of Lead in Various Media to Blood Lead in Human Populations

The various mathematical descriptions of the relationship of blood lead to lead in individual media--air, food, water, dust, soil--were discussed in some detail in Chapter 11 and summarized concisely in a preceding section (1.11) of this chapter. Using values for lead intake/content of those media which appear to represent the current exposure picture for human populations in the U.S., those relationships are further employed in this section to estimate proportional inputs to total blood lead levels in U.S. populations. Such an exercise is of help in providing an overall perspective on which routes of exposure are of most significance in terms of contributions to blood lead levels seen in U.S. populations.

Table 1-16 tabulates the relative direct contributions (in percentages) of air lead to blood lead at different air-lead levels for calculated typical background levels of lead from food and water in adults. The blood lead contributions from diet are estimated using the slope 0.02 µg/dl increase in blood lead µg/day intake as discussed in Section 1.11.3. In Table 1-17 are listed direct contributions of air lead to blood lead at varying air lead levels for children, given calculated typical background levels of blood lead derived from food and water as per the work of Ryu et al. (1983). Table 1-18 shows relative contributions of dust/soil to blood lead at varying dust/soil levels for children given calculated background levels of blood lead from air, food, and water. Assuming that virtually all soil/dust lead is due to atmospheric fallout of lead particles, the percentage contribution of air lead directly and indirectly to blood lead becomes significantly greater than when considering just the direct impact of inhaling lead in the ambient air.

TABLE 1-16. DIRECT CONTRIBUTIONS OF AIR LEAD TO BLOOD LEAD (PbB) IN ADULTS AT FIXED INPUTS OF WATER AND FOOD LEAD

Air Lead ($\mu g/m^3$)	PbB (Air)[a]	PbB (Food)[b]	PbB (Water)[c]	% PbB From Air
0.1	0.2	2.0	0.6	7.1
1.0	2.0	2.0	0.6	43.4
1.5	3.0	2.0	0.6	53.5

[a] $\frac{\Delta \text{ PbB}}{\Delta \text{ Pb Air}} = 2.0$ for 3.2 $\mu g/m^3$ or less.

[b] Assuming 100 µg/day lead from diet and slope 0.02 as discussed in Section 11.4.2.4.

[c] Assuming 10 µg/ℓ water, Pocock et al. (1983).

TABLE 1-17. DIRECT CONTRIBUTIONS OF AIR LEAD TO BLOOD LEAD IN CHILDREN AT FIXED INPUTS OF FOOD AND WATER LEAD

Air Lead ($\mu g/m^3$)	PbB (Air)[a]	PbB (Food)[b]	PbB (Water)[c]	% PbB From Air
0.1	0.2	16.0	0.6	1.2
0.5	1.0	16.0	0.6	5.7
1.0	2.0	16.0	0.6	10.8
1.5	3.0	16.0	0.6	15.3
2.5	5.0	16.0	0.6	23.1

[a] $\frac{\Delta \text{ PbB}}{\Delta \text{ Pb Air}} = 2.0$ for 3.2 $\mu g/m^3$ or less.

[b] Assuming 100 µg Pb/day based upon Ryu et al. (1983).

[c] Assuming 10 µg Pb/l water, using Pocock et al. (1983).

TABLE 1-18. CONTRIBUTIONS OF DUST/SOIL LEAD TO BLOOD LEAD IN CHILDREN AT FIXED INPUTS OF AIR, FOOD, AND WATER LEAD

Dust-Soil (µg/g)	Air Lead $\mu g/m^3$	PbB (Air)[a]	PbB (Food)[b]	PbB (Water)[c]	PbB (Dust-Soil)[d]	% PbB From Dust/Soil
500	0.5	1.0	16.0	0.6	0.3/3.4	1.7/16.2
1000	0.5	1.0	16.0	0.6	0.6/6.8	3.3/27.8
2000	0.5	1.0	16.0	0.6	1.2/13.6	6.4/43.6

[a] $\frac{\Delta \text{ PbB}}{\Delta \text{ Pb Air}} = 2.0$ for 3.2 $\mu g/m^3$ or less.

[b] Assuming 100 µg Pb/day based on Ryu et al. (1983).

[c] Assuming 10 µg Pb/l water, based on Pocock et al. (1983).

[d] Based on range 0.6 to 6.8 µg/dl for 1000 µg/g (Angle and McIntire, 1979).

1.13.4 BIOLOGICAL EFFECTS OF LEAD RELEVANT TO THE GENERAL HUMAN POPULATION

It is clear from the wealth of available literature reviewed in Chapter 12, that there exists a continuum of biological effects associated with lead across a broad range of exposure. At rather low levels of lead exposure, biochemical changes, e.g., disruption of certain enzymatic activities involved in heme biosynthesis and erythropoietic pyrimidine metabolism, are detectable. Heme biosynthesis is a generalized process in mammalian species, including man, with importance for normal physiological functioning of virtually all organ systems. With increasing lead exposure, there are sequentially more intense effects on heme synthesis and a broadening of lead effects to additional biochemical and physiological mechanisms in various tissues, such that increasingly more severe disruption of the normal functioning of many different organ systems becomes apparent. In addition to heme biosynthesis impairment at relatively low levels of lead exposure, disruption of normal functioning of the erythropoietic and the nervous systems are among the earliest effects observed as a function of increasing lead exposure. With increasingly intense exposure, more severe disruption of the erythropoietic and nervous systems occur and additional organ systems are affected so as to result, for example, in the manifestation of renal effects, disruption of reproductive functions, and impairment of immunological functions. At sufficiently high levels of exposure, the damage to the nervous system and other effects can be severe enough to result in death or, in some cases of non-fatal lead poisoning, long-lasting sequelae such as permanent mental retardation.

As discussed in Chapter 12 of this document, numerous new studies, reviews, and critiques concerning Pb-related health effects have been published since the issuance of the earlier EPA lead criteria document in 1977. Of particular importance for present criteria development purposes are those new findings, taken together with information earlier available at the writing of the 1977 Criteria Document, which have bearing on the establishment of quantitative dose-effect or dose-response relationships for biological effects of lead potentially viewed as adverse health effects likely to occur among the general population at or near existing ambient air concentrations of lead in the United States. Key information regarding observed health effects and their implications are discussed below for adults and children.

For the latter group, children, emphasis is placed on the discussion of (1) heme biosynthesis effects, (2) certain other biochemical and hematological effects, and (3) the disruption of nervous system functions. All of these appear to be among those effects of most concern for potential occurrence in association with exposure to existing U.S. ambient air lead levels of the population group (i.e., children ≤6 years old) at greatest risk for lead-induced health effects. Emphasis is also placed on the delineation of internal lead exposure levels, as defined mainly by blood-lead (PbB) levels, likely associated with the occurrence of such effects. Also discussed are characteristics of the subject effects that are of crucial impor-

tance in regard to the determination of which might reasonably be viewed as constituting "adverse health effects" in affected human populations.

1.13.4.1 Criteria for Defining Adverse Health Effects. Over the years, there has been superimposed on the continuum of lead-induced biological effects various judgments as to which specific effects observed in man constitute "adverse health effects". Such judgments involve not only medical concensus regarding the health significance of particular effects and their clinical management, but also incorporate societal value judgments. Such societal value judgments often vary depending upon the specific overall contexts to which they are applied, e.g., in judging permissible exposure levels for occupational versus general population exposures to lead. For some lead exposure effects, e.g., severe nervous system damage resulting in death or serious medical sequelae consequent to intense lead exposure, there exists little or no disagreement as to these being significant "adverse health effects." For many other effects detectable at sequentially lower levels of lead exposure, however, the demarcation lines as to which effects represent adverse health effects and the lead exposure levels at which they are accepted as occurring are neither sharp nor fixed, having changed markedly during the past several decades. That is, from a historical perspective, levels of lead exposure deemed to be acceptable for either occupationally exposed persons or the general population have been steadily revised downward as more sophisticated biomedical techniques have revealed formerly unrecognized biological effects and concern has increased in regard to the medical and social significance of such effects.

It is difficult to provide a definitive statement of all criteria by which specific biological effects associated with any given agent can be judged to be "adverse health effects". Nevertheless, several criteria are currently well-accepted as helping to define which effects should be viewed as "adverse". These include: (1) impaired normal functioning of a specific tissue or organ system itself; (2) reduced reserve capacity of that tissue or organ system in dealing with stress due to other causative agents; (3) the reversibility/irreversibility of the particular effect(s); and (4) the cumulative or aggregate impact of various effects on individual organ systems on the overall functioning and well-being of the individual.

Examples of possible uses of such criteria in evaluating lead effects can be cited for illustrative purposes. For example, impairment of heme synthesis intensifies with increasing lead exposure until hemeprotein synthesis is inhibited in many organ systems, leading to reductions in such functions as oxygen transport, cellular energetics, and detoxification of xenobiotic agents. The latter effect can also be cited as an example of reduced reserve capacity pertinent to consideration of effects of lead, the reduced capacity of the liver to detoxify certain drugs or other xenobiotic agents resulting from lead effects on hepatic detoxification enzyme systems.

In regard to the issue of reversibility/irreversibility of lead effects, there are really two dimensions to the issue that need to be considered, i.e.: (1) biological reversibility or irreversibility characteristic of the particular effect in a given organism; and (2) the generally less-recognized concept of exposure reversibility or irreversibility. Severe central nervous system damage resulting from intense, high level lead exposure is generally accepted as an irreversible effect of lead exposure; the reversibility/irreversibility of certain more difficult-to-detect neurological effects occurring at lower lead exposure levels, however, remains a matter of some controversy. The concept of exposure reversibility/irreversibility can be illustrated by the case of urban children of low socioecomomic status showing disturbances in heme biosynthesis and erythropoiesis. Biologically, these various effects may be considered reversible; the extent to which actual reversibility occurs, however, is determined by the feasibility of removing these subjects from their particular lead exposure setting. If such removal from exposure is unlikely or does not occur, then such effects will logically persist and, defacto, constitute essentially irreversible effects.

1.13.4.2 Dose-Effect Relationships for Lead-Induced Health Effects

Human Adults. Table 1-19 concisely summarizes the lowest observed effect levels (in terms of blood lead concentrations) thus far credibly associated with particular health effects of concern for human adults in relation to specific organ systems or generalized physiological processes, e.g. heme synthesis.

The most serious effects associated with markedly elevated blood lead levels are severe neurotoxic effects that include irreversible brain damage as indexed by the occurrence of acute or chronic encephalopathic symptoms observed in both humans and experimental animals. For most human adults, such damage typically does not occur until blood lead levels exceed 100-120 µg/dl. Often associated with encephalopathic symptoms at such blood lead levels or higher are severe gastrointestinal symptoms and objective signs of effects on several other organ systems as well. The precise threshold for occurrence of overt neurological and gastrointestinal signs and symptoms of lead intoxication remains to be established but such effects have been observed in adult lead workers at blood lead levels as low as 40-60 µg/dl, notably lower than the 60 or 80 µg/dl levels previously established or discussed as being "safe" for occupational lead exposure.

Other types of health effects occur coincident with the above overt neurological and gastrointestinal symptoms indicative of marked lead intoxication. These range from frank peripheral neuropathies to chronic renal nephropathy and anemia. Toward the lower range of blood lead levels associated with overt lead intoxication or somewhat below, less severe but important signs of impairment in normal physiological functioning in several organ systems are evident, including: (1) slowed nerve conduction velocities indicative of peripheral nerve

TABLE 1-19. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN ADULTS

Lowest Observed Effect Level (PbB)	Heme Synthesis and Hematological Effects	Neurological Effects	Renal System Effects	Reproductive Function Effects	Gastrointestinal Effects
100-120 µg/dl		Encephalopathic signs and symptoms	Chronic renal nephropathy		Overt gastrointestinal symptoms (colic, etc.)
80 µg/dl	Frank anemia				
60 µg/dl		?			
50 µg/dl	Reduced hemoglobin production	Overt subencephalopathic neurological symptoms		Altered testicular function	
40 µg/dl	Increased urinary ALA and elevated coproporphyrins	?			
30 µg/dl		Peripheral nerve dysfunction (slowed nerve conduction)			
25-30 µg/dl	Erythrocyte protoporphyrin (EP) elevation in males	?			
15-20 µg/dl	Erythrocyte protoporphyrin (EP) elevation in females				
<10 µg/dl	ALA-D inhibition				

Abbreviations: PbB = blood lead concentrations.

dysfunction (at 30-40 μg/dl, or possibly lower levels); (2) altered testicular function (at 40-50 μg/dl); and (3) reduced hemoglobin production (at approximately 50 μg/dl) and other signs of impaired heme synthesis evident at still lower blood lead levels. All of these effects point toward a generalized impairment of normal physiological functioning across several different organ systems, which becomes abundantly evident as adult blood lead levels approach or exceed 30-40 μg/dl. Evidence for impaired heme synthesis effects in blood cells exists at still lower blood lead levels in human adults and the significance of this and evidence of impairment of other biochemical processes important in cellular energetics are the subject of discussion below in relation to health effects observed in children.

Children. Table 1-20 summarizes lowest observed effect levels for a variety of imporatnt health effects observed in children. Again, as for adults, it can be seen that lead impacts many different organ systems and biochemical/physiological processes across a wide range of exposure levels. Also, again, the most serious of these effects is the severe, irreversible central nervous system damage manifested in terms of encephalopathic signs and symptoms. In children, effective blood lead levels for producing encephalopathy or death are lower than for adults, starting at approximately 80-100 μg/dl. Other overt neurological symptoms are evident at somewhat lower blood lead levels associated with lasting neurological sequalae. Colic and other overt gastrointestinal symptoms clearly occur at similar or still lower blood lead levels in children, at least down to 60 μg/dl and, perhaps, below. Renal dysfunction is also manifested along with the above overt signs of lead intoxication in children and has been reported at blood lead levels as low as 40 μg/dl in some pediatric populations. Frank anemia is also evident at 70 μg/dl, representing an extreme manifestation of reduced hemoglobin synthesis observed at blood lead levels as low as 40 μg/dl along with other signs of marked heme synthesis inhibition at that exposure level. Again, all of these effects are reflective of widespread impact of lead on the normal physiological functioning of many different organ systems in children at blood lead levels at least as low as 40 μg/dl.

Among the most important and controversial of the issues discussed in Chapter 12 are the evaluation of neuropsychological or electrophysiological effects associated with low-level lead exposures in non-overtly lead intoxicated children. None of the available studies on the subject, individually, can be said to prove conclusively that significant neurological effects occur in children at blood-Pb levels <30 μg/dl. The collective neurobehavioral studies of CNS (cognitive; IQ) effects, for example, can probably now be most reasonably interpreted as most clearly being indicative of a likely association between neuropsychologic deficits and low-level Pb-exposures in young children resulting in blood-Pb levels of approximately 30 to 50 μg/dl. However, due to specific methodological problems with each of the various studies (as noted in Chapter 12), much caution is warranted that precludes conclusive acceptance of the

TABLE 1-20. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN CHILDREN

Lowest Observed Effect Level (PbB)	Heme Synthesis and Hematological Effects	Neurological Effects	Renal System Effects	Gastrointestinal Effects	Other Biochemical Effects
80-100 µg/dl		Encephalopathic signs and symptoms	Renal dysfunction (aminoaciduria)	Colic, other overt gastrointestinal symptoms	
70 µg/dl	Frank anemia				
60 µg/dl					
50 µg/dl		↑ 7			
40 µg/dl	Reduced hemoglobin	Cognitive (CNS) deficts			
	Elevated coproporphyrin	Peripheral nerve dysfunction (slowed NCV's)			
	Increased urinary ALA				
30 µg/dl					Vitamin D metabolism interference
15-20 µg/dl	Erythrocyte protoporphyin elevation	CNS electrophysiological deficits			
10	ALA-D inhibition	?			Py-5-N activity inhibition
	?				

Abbreviations: PbB = blood lead concentrations; Py-5-N = pyrimidine-5'-nucleotidase.

observed effects being due to Pb rather than other (at times uncontrolled for) potentially confounding variables.

Also of considerable importance are studies by which provide evidence of changes in EEG brain wave patterns and CNS evoked potential responses in non-overtly lead intoxicated children experiencing relatively low blood-Pb levels. Sufficient exposure information was provided by these studies and appropriate statistical analyses were carried out which demonstrated clear, statistically significant associations between electrophysiological (SW voltage) changes and blood-Pb levels in the range of 30 to 55 μg/dl and probable analogous associations at blood-Pb levels below 30 μg/dl (with no evident threshold down to 15 μg/dl). In this case, the continued presence of such electrophysiological changes upon follow-up two years later, suggests persistence of such effects even in the face of later declines in blood-Pb levels and, therefore, possible non-reversibility of the observed electrophysiological CNS changes. However, the reported electrophysiological effects were not found to be significantly associated with IQ decrements.

The precise medical or health significance of the neuropsychological and electrophysiological effects found by the above studies to be associated with low-level Pb-exposures is difficult to state with confidence at this time. The IQ deficits and other behavioral changes, although statistically significant, are generally relatively small in magnitude as detected by the reviewed studies, but nevertheless may still impact the intellectual development, school performance, and social development of the affected children sufficiently so as to be regarded as adverse. This would be especially true if such impaired intellectual development or school performance and disrupted social development were reflective of persisting, long-term effects of low-level lead exposure in early childhood. The issue of persistence of such lead effects, however, remains to be more clearly resolved, with some study results reviewed in Chapter 12 and mentioned above suggesting that significant low-level Pb-induced neurobehavioral and EEG effects may, in fact, persist into later childhood.

In regard to additional studies reviewed in Chapter 12 concerning the neurotoxicity of lead, certain evidence exists which suggests that neurotoxic effects may be associated with lead-induced altered heme synthesis, which results in an accumulation of ALA in brain affecting CNS GABA synthesis, binding, and/or inactivation by neuronal reuptake after synaptic release. Also, available experimental data suggest that these effects may have functional significance in the terms of this constituting one mechanism by which lead may increase the sensitivity of rats to drug-induced seizures and, possibly, by which GABA-related behavioral or physiological control functions are disrupted. Unfortunately, the available research data do not allow credible direct estimates of blood-lead levels at which such effects might occur in rats, other non-human mammalian species, or man. Inferentially, however, one can state

that threshold levels for any marked lead-induced ALA impact on CNS GABA mechanisms are most probably at least as high as blood-lead levels at which significant accumulations of ALA have been detected in erythrocytes or non-blood soft tissues (see below). Regardless of any dose-effect levels inferred, though, the functional and/or medical significance of lead-induced ALA effects on CNS mechanisms at low-levels of lead-exposure remains to be more fully determined and cannot, at this time, be unequivocably seen as an adverse health effect.

Research concerning lead-induced effects on heme synthesis, also provides information of importance in evaluating whether significant health effects in children are associated with blood-lead levels below 30 μg/dl. As discussed earlier, lead affects heme synthesis at several points in its metabolic pathway, with consequent impact on the normal functioning of many body tissues. The activity of the enzyme, ALA-S, catalyzing the rate-limiting step of heme synthesis does not appear to be significantly affected until blood-lead levels reach or exceed approximately 40 μg/dl. The enzyme ALA-D, which catalizes the conversion of ALA to porphobilinogen as a further step in the heme biosynthetic pathway, appears to be affected at much lower blood-lead levels as indexed directly by observations of ALA-D inhibition or indirectly in terms of consequent accumulations of ALA in blood and non-blood tissues. More specifically, inhibition of erythrocyte ALA-D activity has been observed in humans and other mammalian species at blood-lead levels even below 10 to 15 μg/dl, with no clear threshold evident. Correlations between erythrocyte and hepatic ALA-D activity inhibition in lead workers at blood-lead levels in the range of 12 to 56 μg/dl suggest that ALA-D activity in soft tissues (eg. brain, liver, kidney, etc.) may be inhibited at similar blood-lead levels at which erythrocyte ALA-D activity inhibition occurs, resulting in accumulations of ALA in both blood and soft tissues.

It is now clear that significant increases in both blood and urinary ALA occur below the currently commonly-accepted blood-lead level of 40 μg/dl and, in fact, such increases in blood and urinary ALA are detectable in humans at blood-lead levels below 30 μg/dl, with no clear threshold evident down to 15 to 20 μg/dl. Other studies have demonstrated significant elevations in rat brain, spleen and kidney ALA levels consequent to acute or chronic lead-exposure, but no clear blood-lead levels can yet be specified at which such non-blood tissue ALA increases occur in humans. It is reasonable to assume, however, that ALA increases in non-blood tissues likely begin to occur at roughly the same blood-lead levels associated with increases in erythrocyte ALA levels.

Lead also affects heme synthesis beyond metabolic steps involving ALA, leading to the accumulation of protoporphyrin in erythrocytes as the result of impaired iron insertion into the porphyrin moiety to form heme. The porphyrin acquires a zinc ion in lieu of the native iron, and the resulting accumulation of blood zinc protoporphyrin (ZPP) tightly bound to erythrocytes for their entire life (120 days) represents a commonly employed index of lead-

exposure for medical screening purposes. The threshold for elevation of erythrocyte protoporphyrin (EP) levels is well-established as being 25 to 30 μg/dl in adults and approximately 15 μg/dl for young children, with significant EP elevations (>1 to 2 standard deviations above reference normal EP mean levels) occurring in 50 percent of all children studied as blood-lead levels approach or moderately exceed 30 μg/dl.

Medically, small increases in EP levels have generally not been viewed as being of great concern at initial detection levels around 15 to 20 μg/dl in children, but EP increases become more worrisome as markedly greater, significant EP elevations occur as blood-lead levels approach and exceed 30 μg/dl and additional signs of significantly deranged heme synthesis begin to appear along with indications of functional disruption of various organ systems. Previously, such other signs of significant organ system functional disruptions had only been credibly detected at blood-lead levels somewhat in excess of 30 μg/dl, e.g., hemoglobin synthesis inhibition starting at 40 μg/dl and significant nervous system effects at 50-60 μg/dl. This served as a basis for CDC establishment of 30 μg/dl blood-lead as a criteria level for undue lead exposure for young children and adoption by EPA of it as the "maximum safe" blood-lead level (allowing some margin of safety before reaching levels associated with inhibition of hemoglobin synthesis or nervous system deficits) in setting the 1978 NAAQS for lead.

To the extent that new evidence is now available, indicative of probable lead effects on nervous system functioning or other important physiological processes at blood-lead levels below 30 to 40 μg/dl, then the rationale for continuing to view 30 μg/dl as a "maximum safe" blood-lead level is called into question and substantial impetus is provided for revising the criteria level downward, i.e., to some blood-lead level below 30 μg/dl. At this time, such impetus toward revising the blood-lead criteria level downward is gaining momentum not only from new neuropsychologic and electrophysiological findings of the type summarized above, but also from growing evidence for lead effects on other functional systems. These include, for example, the: (1) disruption of formation of the heme-containing protein, cytochrome c, of considerable importance in cellular energetics involved in mediation of the normal functioning of many different mammalian (including human) organ systems and tissues; (2) inhibition by lead of the biosynthesis of globin, the protein moiety of hemoglobin, in the presense of lead at concentrations corresponding to a blood-lead level of 20 μg/dl; (3) observations of significant inhibition of pyrimidine-5'-nucleotidase (Py-5-N) activity in adults at blood-lead levels ≥44 μg/dl and in children down to blood-lead levels of 10 μg/dl; and (4) observations of lead interference with vitamin D metabolism in children across a blood-lead level range of 33 to 120 μg/dl, with consequent increasingly enhanced lead uptake due to decreased vitamin D metabolism and likely associated increasingly cascading effects on nervous system and other functions at sequentially higher blood-lead levels. Certain additional evidence for lead effects on hormonal systems and immune system components, thus far detected only at relatively

high blood-lead levels or at least not credibly associated with blood-lead levels as low as 30 to 40 µg/dl, also contributes to concern as blood-lead levels exceed 30 µg/dl.

Also adding to the concern about relatively low lead exposure levels are the results of an expanding array of animal toxicology studies which demonstrate: (1) persistence of lead-induced neurobehavioral alterations well into adulthood long after termination of perinatal lead exposure early in development of several mammalian species; (2) evidence for uptake and retention of lead in neural and non-neuronal elements of the CNS, including long-term persistence in brain tissues after termination of external lead exposure and blood lead levels return to "normal"; and (3) evidence from various in-vivo and in-vitro studies indicating that, at least on a subcellular-molecular level, no threshold may exist for certain neurochemical effects of lead.

1.13.5 DOSE-RESPONSE RELATIONSHIPS FOR LEAD EFFECTS IN HUMAN POPULATIONS

Information summarized in the preceding section dealt with the various biological effects of lead germane to the general population and included comments about the various levels of blood lead observed to be associated with the measurable onset of these effects in various populations groups.

A number of investigators have attempted to quantify more precisely dose-population response relationships for some of the above lead effects in human populations. That is they have attempted to define the proportion of a population exhibiting a particular effect at a given blood lead level. To date, such efforts at defining dose-response relationships for lead effects have been mainly limited to the following effects of lead on heme biosynthesis: inhibition of ALA-D activity; elevation of EP; and urinary excretion of ALA.

Dose-population response relationships for EP in children has been analyzed in detail by Piomelli and et al. (1982) and the corresponding plot at 2 levels of elevation (>1 S.D., >2 S.D.) is shown in Figure 1-19 using probit analysis. It can be seen that blood lead levels in half of the children showing EP elevations at >1 and 2 S.D.'s closely bracket the blood lead level taken as the high end of "normal" (i.e., 30 µg/dl). Dose-response curves for adult men and women as well as children prepared by Roels et al. (1976) are set forth in Figure 1-20. In Figure 1-20, it may be seen that the dose-response for children remains greater across the blood-lead range studied, followed by women, then adult males.

Figure 1-21 presents dose-population response data for urinary ALA exceeding two levels (at mean + 1 S.D. and mean + 2 S.D.), as calculated by EPA from the data of Azar et at. (1975). The percentages of the study populations exceeding the corresponding cut-off levels as calculated by EPA for the Azar data are set forth in Table 1-21. It should be noted that the measurement of ALA in the Azar et al. study did not account for amino acetone, which may influence the results observed at the lowest blood lead levels.

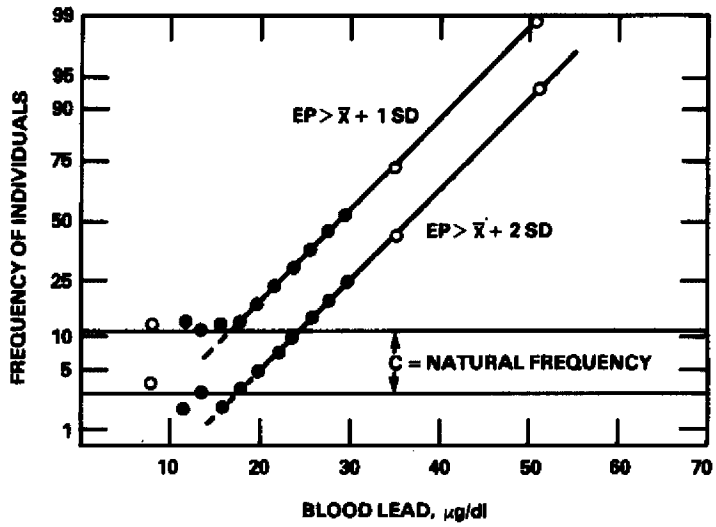

Figure 1-19. Dose-response for elevation of EP as a function of blood lead level using probit analysis. Geometric mean plus 1 S.D. = 33 μg/dl; geometric mean plus 2 S.D. = 53 μg/dl.

Source: Piomelli et al. (1982).

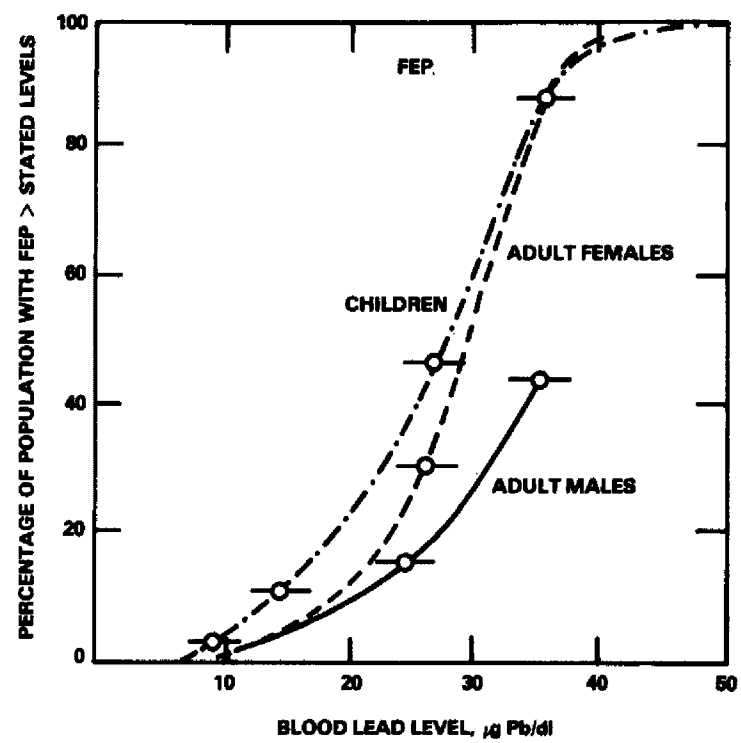

Figure 1-20. Dose-response curve for FEP as a function of blood lead level: in subpopulations.

Source: Roels et al. (1976).

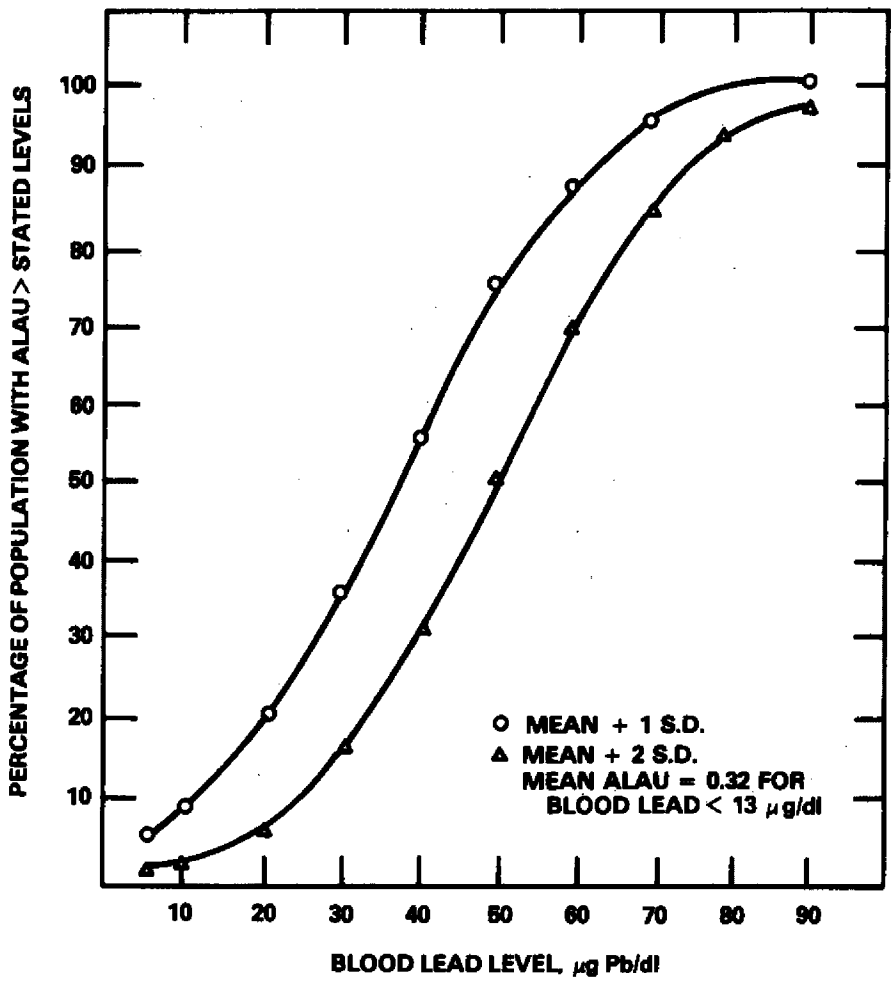

Figure 1-21. EPA calculated dose-response curve for ALA-U.

Source: Azar et al. (1975).

TABLE 1-21. EPA-ESTIMATED PERCENTAGE OF SUBJECTS WITH ALA-U EXCEEDING LIMITS FOR VARIOUS BLOOD LEAD LEVELS

Blood lead levels (μg/dl)	Azar et al. (1975) (Percent Population)
10	2
20	6
30	16
40	31
50	50
60	69
70	84

1.13.6 POPULATIONS AT RISK

Population at risk is a segment of a defined population exhibiting characteristics associated with significantly higher probability of developing a condition, illness, or other abnormal status. This high risk may result from either (1) greater inherent susceptibility or (2) from exposure situations peculiar to that group. What is meant by inherent susceptibility is a host characteristic or status that predisposes the host to a greater risk of heightened response to an external stimulus or agent.

In regard to lead, two such populations are definable. They are preschool age children, especially those living in urban settings, and pregnant women, the latter group owing mainly to the risk to the conceptus. Children are such a population for both of the reasons stated above, whereas pregnant women are at risk primarily due to the inherent susceptibility of the conceptus.

1.13.6.1 Children as a Population at Risk. Children are developing and growing organisms exhibiting certain differences from adults in terms of basic physiologic mechanisms, capability of coping with physiologic stress, and their relative metabolism of lead. Also, the behavior of children frequently places them in different relationship to sources of lead in the environment, thereby enhancing the opportunity for them to absorb lead. Furthermore, the occurrence of excessive exposure often is not realized until serious harm is done. Young children do not readily communicate a medical history of lead exposure, the early signs of such being common to so many other disease states that lead is frequently not recognized early on as a possible etiological factor contributing to the manifestation of other symptoms.

Inherent Susceptibility of the Young. Discussion of the physiological vulnerability of the young must address two discrete areas. Not only should the basic physiological differences be considered that one would expect to predispose children to a heightened vulnerability to lead, but also the actual clinical evidence must be considered that shows such vulnerability does indeed exist.

In Chapter 10 and Section 1.13.2 above, differences in relative exposure to lead and body handling of lead for children versus adults were pinpointed throughout the text. The significant elements of difference include: (1) greater intake of lead by infants and young children into the respiratory and gastro-intestinal tracts on a body weight basis compared to adults; (2) greater absorption and retention rates of lead in children; (3) much greater prevalence of nutrient deficiency in the case of nutrients which affect lead absorption rates from the GI tract; (4) differences in certain habits, i.e., normal hand to mouth activity as well as pica resulting in the transfer of lead-contaminated dust and dirt to the GI tract; (5) differences in the efficiency of lead sequestration in the bones of children, such that not only is less of the body burden of lead in bone at any given time but the amount present may be relatively more labile. Additional information discussed in Chapter 12 suggests that the blood-brain

barrier in children is less developed, posing the risk for greater entry of lead into the nervous system.

Hematological and neurological effects in children have been demonstrated to have lower thresholds in terms of blood lead levels than in adults. The extent of reduced hemoglobin production and EP accumulation occur at relatively lower exposure levels in children than in adults, as indexed by blood lead thresholds. With reference to neurologic effects, the onset of encephalopathy and other injury to the nervous system appears to vary both regarding likely lower thresholds in children for some effects and in the typical pattern of neurologic effects presented, e.g., in encephalopathy or other CNS deficits being more common in children versus peripheral neuropathy being more often seen in adults. Not only are the effects more acute in children than in adults, but also the neurologic sequelae are usually much more severe in children.

Exposure Consideration. The dietary habits of children as well as the diets themselves differ markedly from adults and, as a result, place children in a different relationship to several sources of lead. The dominance of canned milk and processed baby food in the diet of many young children is an important factor in assessing their exposure to lead since both those foodstuffs have been shown to contain higher amounts of lead than components of the adult diet. The importance of these lead sources is not their relationship to airborne lead directly but, rather, their role in providing a higher baseline lead burden to which the airborne contribution is added.

Children ordinarily undergo a stage of development in which they exhibit normal mouthing behavior, as manifested, for example, in the form of thumbsucking. At this time they are at risk for picking up lead-contaminated soil and dust on their hands and hence into their mouths where it can be absorbed. Scientific evidence documenting at least the first part of the chain is available.

There is, however, an abnormal extension of mouthing behavior, called pica, which occurs in some children. Although diagnosis of this is difficult, children who exhibit this trait have been shown to purposefully eat nonfood items. Much of the lead-based paint problem is known to occur because children actively ingest chips of leaded paint.

1.13.6.2 Pregnant Women and the Conceptus as a Population at Risk. There are some rather inconculsive data indicating that women may in general be somewhat higher risk to lead than men. However, pregnant women and their concepti as a subgroup are demonstrably at higher risk. It should be pointed out that, in fact, it really is not the pregnant woman per se who is at greatest risk but, rather, the unborn child she is carrying. Because of obstetric complications, however, the mother herself can also be at somewhat greater risk at the time of delivery of her child.

Studies have demonstrated that women in general, like children, tend to show a heightened response of erythorcyte protoporphyrin levels upon exposure to lead. The exact reason for this heightened response is not known but may relate to endocrine differences between men and women.

As stated above, the primary reason pregnant women are a high-risk group is because of the fetus each is carrying. In addition, there is some suggestive evidence that lead exposures may also affect maternal complications at delivery. With reference to maternal complication at delivery, information in the literature suggests that the incidence of preterm delivery and premature membrane rupture relates to maternal blood lead level. Further study of this relationship as well as studies relating to discrete health effects in the newborn are needed.

Vulnerability of the developing fetus to lead exposure arising from transplacental transfer of maternal lead was discussed in Chapter 10. This process starts at the end of the first trimester. Umbilical cord blood studies involving mother-infant pairs have repeatedly shown a correlation between maternal and fetal blood lead levels.

Further suggestive evidence, cited in Chapter 12, has been advanced for prenatal lead exposures of fetuses possibly leading to later higher instances of postnatal mental retardation among the affected offspring. The available data are insufficient to state with any certainty that such effects occur or to determine with any precision what levels of lead exposure might be required prior to or during pregnancy in order to produce such effects.

1.13.6.3 Description of the United States Population in Relation to Potential Lead Exposure Risk

In this section, estimates are provided of the number of individuals in those segments of the population which have been defined as being potentially at greatest risk for lead exposures. These segments include pre-school children (up to 6 years of age), especially those living in urban settings, and women of child-bearing age (defined here as ages 15-44). These data, which are presented below in Table 1-22, were obtained from a provisional report by the U.S. Census Bureau (1982), which indicates that approximately 61 percent of the populace lives in urban areas (defined as central cities and urban fringe). Assuming that the 61 percent estimate for urban residents also applies to children of preschool age, then approximately 14,206,000 children of the total listed in Table 1-22 would be expected to be at greater risk by virtue of higher lead exposures generally associated with their living in urban versus non-urban settings. (NOTE: The age distribution of the percentage of urban residents may vary between SMSA's.)

The risk encountered with exposure to lead may be compounded by nutritional deficits (see Chapter 10). The most commonly seen of these is iron deficiency, especially in young children less than 5 years of age (Mahaffey and Michaelson, 1980). Data available from the National

TABLE 1-22. PROVISIONAL ESTIMATE OF THE NUMBER OF INDIVIDUALS IN URBAN AND RURAL POPULATION SEGMENTS AT GREATEST POTENTIAL RISK TO LEAD EXPOSURE

Population Segment	Actual Age (year)	Total Number in U.S. Population (1981)	Urban Population[1]
Pre-school children	0-4	16,939,000	10,333,000
	5	3,201,000	1,953,000
	6	3,147,000	1,920,000
Total		23,287,000	14,206,000
Women of child-bearing age	15-19	10,015,000	6,109,000
	20-24	10,818,000	6,599,000
	25-29	10,072,000	6,144,000
	30-34	9,463,000	5,772,000
	35-39	7,320,000	4,465,000
	40-44	6,147,000	3,749,000
Total		53,835,000	32,838,000

Source: U.S. Census Bureau (1982), Tables 18 and 31.

[1]An urban/total ratio of 0.61 was used for all age groups. "Urban" includes central city and urban fringe populations.

Center for Health Statistics for 1976-1980 (Fulwood et al., 1982) indicate that from 8 to 22 percent of children aged 3-5 may exhibit iron deficiency, depending upon whether this condition is defined as serum iron concentration (<40 μg/dl) or as transferrin saturation (<16 percent), respectively. Hence, of the 20,140,000 children ≤5 years of age (Table 1-22), as many as 4,431,000 would be expected to be at increased risk depending on their exposure to lead, due to iron deficiency.

As pointed out in Section 1.13.7, the risk to pregnant women is mainly due to risk to the conceptus. By dividing the total number of women of child-bearing age in 1981 (53,835,000) into the total number of live births in 1981 (3,646,000; National Center for Health Statistics, 1982), it may be seen that approximately 7 percent of this segment of the population may be at increased risk at any given time.

1.13.7 SUMMARY AND CONCLUSIONS

Among the most significant pieces of information and conclusions that emerge from the present human health risk evaluation are the following:

(1) Anthropogenic activity has clearly led to vast increases of lead input into those environmental compartments which serve as media (e.g., air, water, food, etc.) by which significant human exposure to lead occurs.

(2) Emission of lead into the atmosphere, especially through leaded gasoline combustion, is of major significance in terms of both the movement of lead to other environmental compartments and the relative impact of such emissions on the internal lead burdens in industrialized human populations. By means of both mathematical modeling of available clinical/epidemiological data by EPA and the isotopic tracing of lead from gasoline to the atmosphere to human blood of exposed populations, the size of atmospheric lead contribution can be confidently said to be 25-50 percent or, probably somewhat higher.

(3) Given this magnitude of relative contribution to human external and internal exposure, reduction in levels of atmospheric lead would then result in significant widespread reductions in levels of lead in human blood (an outcome which is supported by careful analysis of the NHANES II study data). Reduction of lead in food (added in the course of harvesting, transport, and processing) would also be expected to produce significant widespread reductions in human blood lead levels in the United States.

(4) A number of adverse effects in humans and other species are clearly associated with lead exposure and, from a historical perspective, the observed "thresholds" for these various effects (particularly neurological and heme biosynthesis effects) continue to decline as more sophisticated experimental and clinical measures are employed to detect more subtle, but still significant effects. These include significant alterations in normal physiological functions at blood lead levels markedly below the currently accepted 30 µg/dl "maxim safe level" for pediatric exposures.

(5) Several chapters of this document demonstrate that young children are at greatest risk for experiencing lead-induced health effects, particularly in the urbanized, low income segments of this pediatric population. A second group at increased risk are pregnant women, because of exposure of the fetus to lead in the absence of any effective biological (e.g. placental) barrier during gestation.

(6) Dose-population response information for heme synthesis effects, coupled with information from various blood lead surveys, e.g. the NHANES II study, indicate that large numbers of American children (especially low income, urban dwellers) have blood lead levels sufficiently high (in excess of 15-20 µg/dl) that they are clearly at risk for deranged heme synthesis and, possibly, other health effects of growing concern as lead's role as a general systemic toxicant becomes more fully understood.

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Volume II of IV

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Environmental Criteria and Assessment Office
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ABSTRACT

The document evaluates and assesses scientific information on the health and welfare effects associated with exposure to various concentrations of lead in ambient air. The literature through 1983 has been reviewed thoroughly for information relevant to air quality criteria, although the document is not intended as a complete and detailed review of all literature pertaining to lead. An attempt has been made to identify the major discrepancies in our current knowledge and understanding of the effects of these pollutants.

Although this document is principally concerned with the health and welfare effects of lead, other scientific data are presented and evaluated in order to provide a better understanding of this pollutant in the environment. To this end, the document includes chapters that discuss the chemistry and physics of the pollutant; analytical techniques; sources, and types of emissions; environmental concentrations and exposure levels; atmospheric chemistry and dispersion modeling; effects on vegetation; and respiratory, physiological, toxicological, clinical, and epidemiological aspects of human exposure.

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LIST OF ABBREVIATIONS (continued).

sIg	Surface immunoglobulin
SLAMS	State and local air monitoring stations
SMR	Standardized mortality ratio
Sr	Strontium
SRBC	Sheep red blood cells
SRMs	Standard reference materials
STEL	Short-term exposure limit
SW voltage	Slow-wave voltage
T-cells	Thymus-derived lymphocytes
t-tests	Tests of significance
TBL	Tri-n-butyl lead
TEA	Tetraethyl-ammonium
TEL	Tetraethyllead
TIBC	Total iron binding capacity
TML	Tetramethyllead
TMLC	Tetramethyllead chloride
TSH	Thyroid-stimulating hormone
TSP	Total suspended particulate
U.K.	United Kingdom
UMP	Uridine monophosphate
USPHS	U.S. Public Health Service
VA	Veterans Administration
V_d	Deposition velocity
VER	Visual evoked response
WHO	World Health Organization
XRF	X-Ray fluorescence
X^2	Chi squared
Zn	Zinc
ZPP	Erythrocyte zinc protoporphyrin

MEASUREMENT ABBREVIATIONS

dl	deciliter
ft	feet
g	gram
g/gal	gram/gallon
g/ha·mo	gram/hectare·month
km/hr	kilometer/hour
l/min	liter/minute
mg/km	milligram/kilometer
$\mu g/m^3$	microgram/cubic meter
mm	millimeter
µmol	micrometer
ng/cm^2	nanograms/square centimeter
nm	namometer
nM	nanomole
sec	second

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LIST OF ABBREVIATIONS

AAS	Atomic absorption spectrometry
Ach	Acetylcholine
ACTH	Adrenocoticotrophic hormone
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADP/O ratio	Adenosine diphosphate/oxygen ratio
AIDS	Acquired immune deficiency syndrome
AIHA	American Industrial Hygiene Association
AII	Angiotensin II
ALA	Aminolevulinic acid
ALA-D	Aminolevulinic acid dehydrase
ALA-S	Aminolevulinic acid synthetase
ALA-U	Aminolevulinic acid in urine
APDC	Ammonium pyrrolidine-dithiocarbamate
APHA	American Public Health Association
ASTM	Amercian Society for Testing and Materials
ASV	Anodic stripping voltammetry
ATP	Adenosine triphosphate
B-cells	Bone marrow-derived lymphocytes
Ba	Barium
BAL	British anti-Lewisite (AKA dimercaprol)
BAP	benzo(a)pyrene
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
BW	Body weight
C.V.	Coefficient of variation
CaBP	Calcium binding protein
CaEDTA	Calcium ethylenediaminetetraacetate
CBD	Central business district
Cd	Cadmium
CDC	Centers for Disease Control
CEC	Cation exchange capacity
CEH	Center for Environmental Health
CFR	reference method
CMP	Cytidine monophosphate
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CP-U	Urinary coproporphyrin
C_{pah}	plasma clearance of p-aminohippuric acid
Cu	Copper
D.F.	Degrees of freedom
DA	Dopamine
DCMU	[3-(3,4-dichlorophenyl)-1,1-dimethylurea
DDP	Differential pulse polarography
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
EEC	European Economic Community
EEG	Electroencephalogram
EMC	Encephalomyocarditis
EP	Erythrocyte protoporphyrin
EPA	U.S. Environmental Protection Agency

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LIST OF ABBREVIATIONS (continued)

NA	Not Applicable
NAAQS	National ambient air quality standards
NADB	National Aerometric Data Bank
NAMS	National Air Monitoring Station
NAS	National Academy of Sciences
NASN	National Air Surveillance Network
NBS	National Bureau of Standards
NE	Norepinephrine
NFAN	National Filter Analysis Network
NFR-82	Nutrition Foundation Report of 1982
NHANES II	National Health Assessment and Nutritional Evaluation Survey II
Ni	Nickel
OSHA	Occupational Safety and Health Administration
P	Potassium
p	Significance symbol
PAH	Para-aminohippuric acid
Pb	Lead
PBA	Air lead
$Pb(Ac)_2$	Lead acetate
PbB	concentration of lead in blood
PbBrCl	Lead (II) bromochloride
PBG	Porphobilinogen
PFC	Plaque-forming cells
pH	Measure of acidity
PHA	Phytohemagglutinin
PHZ	Polyacrylamide-hydrous-zirconia
PIXE	Proton-induced X-ray emissions
PMN	Polymorphonuclear leukocytes
PND	Post-natal day
PNS	Peripheral nervous system
ppm	Parts per million
PRA	Plasma renin activity
PRS	Plasma renin substrate
PWM	Pokeweed mitogen
Py-5-N	Pyrimide-5'-nucleotidase
RBC	Red blood cell; erythrocyte
RBF	Renal blood flow
RCR	Respiratory control ratios/rates
redox	Oxidation-reduction potential
RES	Reticuloendothelial system
RLV	Rauscher leukemia virus
RNA	Ribonucleic acid
S-HT	Serotonin
SA-7	Simian adenovirus
scm	Standard cubic meter
S.D.	Standard deviation
SDS	Sodium dodecyl sulfate
S.E.M.	Standard error of the mean
SES	Socioeconomic status
SGOT	Serum glutamic oxaloacetic transaminase

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via all routes and averaged over a suitable time period, and the biological responses to those levels be carefully assessed. Assessment of exposure must take into consideration the temporal and spatial distribution of lead and its various forms in the environment.

This document focuses primarily on lead as found in its various forms in the ambient atmosphere; in order to assess its effects on human health, however, the distribution and biological availability of lead in other environmental media have been considered. The rationale for structuring the document was based primarily on the two major questions of exposure and response. The first portion of the document is devoted to lead in the environment--its physical and chemical properties; the monitoring of lead in various media; sources, emissions, and concentrations of lead; and the transport and transformation of lead within environmental media. The later chapters are devoted to discussion of biological responses and effects on ecosystems and human health.

In order to facilitate printing, distribution, and review of the present draft materials, this First External Review Draft of the revised EPA Air Quality Criteria Document for Lead is being released in the form of four volumes. The first volume (Volume I) contains the executive summary and conclusions chapter (Chapter 1) for the entire document. Volume II (the present volume) contains Chapters 2-8, which include: the introduction for the document (Chapter 2); discussions of the above listed topics concerning lead in the environment (Chapters 3-7); and evaluation of lead effects on ecosystems (Chapter 8). The remaining two volumes contain Chapters 9-13, which deal with the extensive available literature relevant to assessment of health effects associated with lead exposure.

An effort has been made to limit the document to a highly critical assessment of the scientific data base. The scientific literature has been reviewed through June 1983. The references cited do not constitute an exhaustive bibliography of all available lead-related literature but they are thought to be sufficient to reflect the current state of knowledge on those issues most relevant to the review of the air quality standard for lead.

The status of control technology for lead is not discussed in this document. For information on the subject, the reader is referred to appropriate control technology documentation published by the Office of Air Quality Planning and Standards (OAQPS), EPA. The subject of adequate margin of safety stipulated in Section 108 of the Clean Air Act also is not explicity addressed here; this topic will be considered in depth by EPA's Office of Air Quality Planning and Standards in documentation prepared as a part of the process of revising the National Ambient Air Quality Standard for Lead.

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TABLE 3-1. PROPERTIES OF ELEMENTAL LEAD

Property	Description
Atomic weight	207.19
Atomic number	82
Oxidation states	+2, +4
Density	11.35 g/cm^3 at 20 °C
Melting point	327.5 °C
Boiling point	1740 °C
Covalent radius (tetradehral)	1.44 Å
Ionic radii	1.21 Å (+2), 0.78 Å (+4)
Resistivity	21.9×10^{-6} ohm/cm

Natural lead is a mixture of four stable isotopes: ^{204}Pb (~1.5 percent), ^{206}Pb (23.6 percent), ^{207}Pb (22.6 percent), and ^{208}Pb (52.3 percent). There is no radioactive progenitor for ^{204}Pb, but ^{206}Pb, ^{207}Pb, and ^{208}Pb are produced by the radioactive decay of ^{238}U, ^{235}U, and ^{232}Th, respectively. There are four radioactive isotopes of lead that occur as members of these decay series. Of these, only ^{210}Pb is long lived, with a half-life of 22 years. The others are ^{211}Pb (half-life 36.1 min), ^{212}Pb (10.64 hr), and ^{214}Pb (26.8 min). The stable isotopic compositions of naturally occurring lead ores are not identical, but show variations reflecting geological evolution (Russell and Farquhar, 1960). Thus, the observed isotopic ratios depend upon the U/Pb and Th/Pb ratios of the source from which the ore is derived and the age of the ore deposit. The $^{206}Pb/^{204}Pb$ isotopic ratio, for example, varies from approximately 16.5 to 21 depending on the source (Doe, 1970). The isotopic ratios in average crustal rock reflect the continuing decay of uranium and thorium. The differences between crustal rock and ore bodies, and between major ore bodies in various parts of the world, often permit the identification of the source of lead in the environment.

3.3 GENERAL CHEMISTRY OF LEAD

Lead is the heaviest element in Group IVB of the periodic table; this is the group that also contains carbon, silicon, germanium, and tin. Unlike the chemistry of carbon, however, the inorganic chemistry of lead is dominated by the divalent (+2) oxidation state rather than

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The methyl compound, TML, is also manufactured by a Grignard process involving the electrolysis of lead pellets in methylmagnesium chloride (Shapiro and Frey, 1968):

$$2CH_3MgCl + 2CH_3Cl + Pb \rightarrow (CH_3)_4Pb + 2MgCl_2 \quad (3\text{-}2)$$

A common type of commercial antiknock mixture contains a chemically redistributed mixture of alkyllead compounds. In the presence of Lewis acid catalysts, a mixture of TEL and TML undergoes a redistribution reaction to produce an equilibrium mixture of the five possible tetraalkyllead compounds. For example, an equimolar mixture of TEL and TML produces a product with a composition as shown below:

Component	Mol percent
$(CH_3)_4Pb$	4.6
$(CH_3)_3Pb(C_2H_5)$	24.8
$(CH_3)_2Pb(C_2H_5)_2$	41.2
$(CH_3)Pb(C_2H_5)_3$	24.8
$(C_2H_5)_4Pb$	4.6

These lead compounds are removed from internal combustion engines by a process called lead scavenging, in which they react in the combustion chamber with halogenated hydrocarbon additives (notably ethylene dibromide and ethylene dichloride) to form lead halides, usually bromochlorolead(II). Mobile source emissions are discussed in detail in Section 5.3.3.2.

Several hundred other organolead compounds have been synthesized, and the properties of many of them are reported by Shapiro and Frey (1968). The continuing importance of organolead chemistry is demonstrated by a variety of recent publications investigating the syntheses (Hager and Huber, 1980, Wharf et al., 1980) and structures (Barkigia, et al., 1980) of organolead complexes, and by recent patents for lead catalysts (Nishikido, et al., 1980).

3.5 FORMATION OF CHELATES AND OTHER COMPLEXES

The bonding in organometallic derivatives of lead is principally covalent rather than ionic because of the small difference in the electronegativities of lead (1.8) and carbon (2.6). As is the case in virtually all metal complexes, however, the bonding is of the donor-acceptor type, in which both electrons in the bonding orbital originate from the carbon atom.

The donor atoms in a metal complex could be almost any basic atom or molecule; the only requirement is that a donor, usually called a ligand, must have a pair of electrons available

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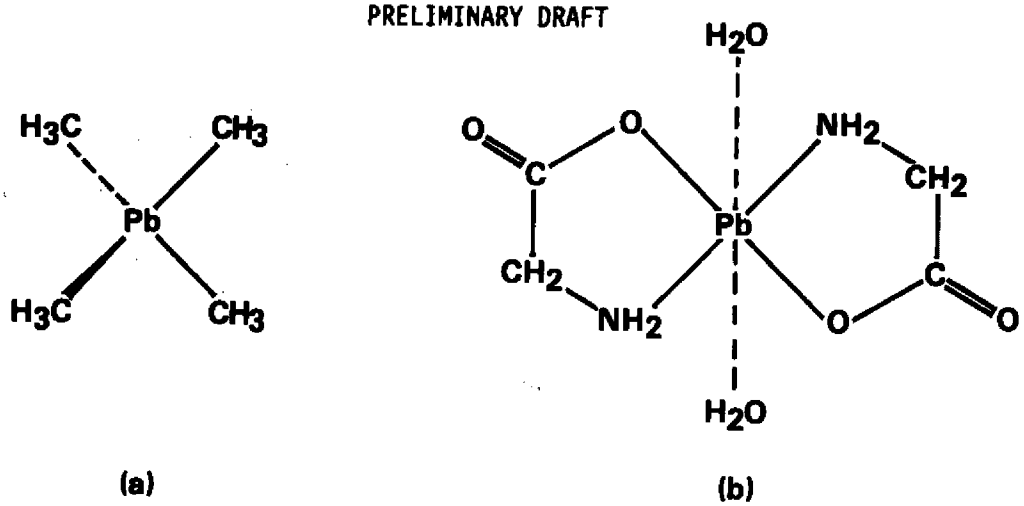

Figure 3-1. Metal complexes of lead.

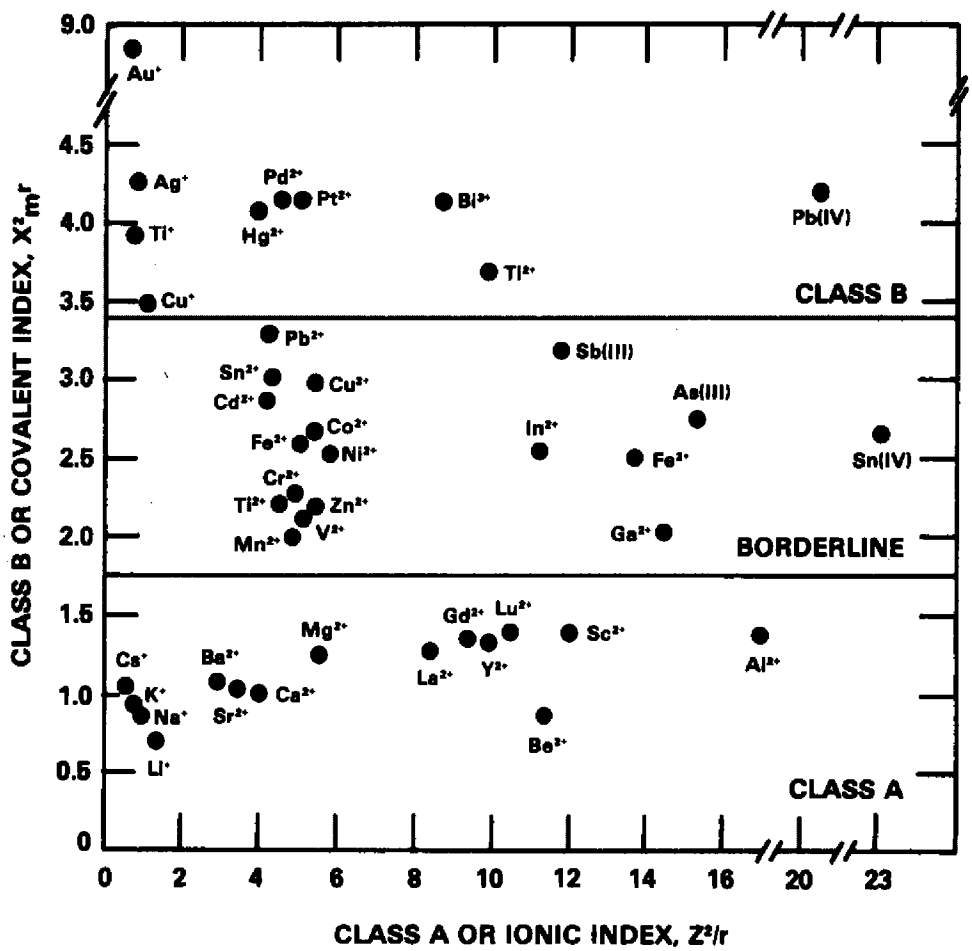

Figure 3-2. Softness parameters of metals.

Source: Nieboer and Richardson (1980).

2. INTRODUCTION

According to Section 108 of the Clean Air Act of 1970, as amended in June 1974, a criteria document for a specific pollutant or class of pollutants shall

> . . . accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities.

Air quality criteria are of necessity based on presently available scientific data, which in turn reflect the sophistication of the technology used in obtaining those data as well as the magnitude of the experimental efforts expended. Thus air quality criteria for atmospheric pollutants are a scientific expression of current knowledge and uncertainties. Specifically, air quality criteria are expressions of the scientific knowledge of the relationships between various concentrations--averaged over a suitable time period--of pollutants in the same atmosphere and their adverse effects upon public health and the environment. Criteria are issued to help make decisions about the need for control of a pollutant and about the development of air quality standards governing the pollutant. Air quality criteria are descriptive; that is, they describe the effects that have been observed to occur as a result of external exposure at specific levels of a pollutant. In contrast, air quality standards are prescriptive; that is, they prescribe what a political jurisdiction has determined to be the maximum permissible exposure for a given time in a specified geographic area.

In the case of criteria for pollutants that appear in the atmosphere only in the gas phase (and thus remain airborne), the sources, levels, and effects of exposure must be considered only as they affect the human population through inhalation of or external contact with that pollutant. Lead, however, is found in the atmosphere primarily as inorganic particulate, with only a small fraction normally occurring as vapor-phase organic lead. Consequently, inhalation and contact are but two of the routes by which human populations may be exposed to lead. Some particulate lead may remain suspended in the air and enter the human body only by inhalation, but other lead-containing particles will be deposited on vegetation, surface waters, dust, soil, pavements, interior and exterior surfaces of housing--in fact, on any surface in contact with the air. Thus criteria for lead must be developed that will take into account all principal routes of exposure of the human population.

This criteria document is a revision of the previous Air Quality Criteria Document for Lead (EPA-600/8-77-017) published in December, 1977. This revision is mandated by the Clean Air Act (Sect. 108 and 109), as amended U.S.C. §§7408 and 7409. The criteria document sets forth what is known about the effects of lead contamination in the environment on human health and welfare. This requires that the relationship between levels of exposure to lead,

3.6 REFERENCES

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3. CHEMICAL AND PHYSICAL PROPERTIES

3.1 INTRODUCTION

Lead is a gray-white metal of bright luster that, because of its easy isolation and low melting point (327.5°C), was among the first of the metals to be placed in the service of man. Lead was used as early as 2000 B.C. by the Phoenicians, who traveled as far as Spain and England to mine it, and it was used extensively by the Egyptians; the British Museum contains a lead figure found in an Egyptian temple which possibly dates from 3000 B.C. The most abundant ore is galena, in which lead is present as the sulfide (PbS), and from which metallic lead is readily smelted. The metal is soft, malleable, and ductile, a poor electrical conductor, and highly impervious to corrosion. This unique combination of physical properties has led to its use in piping and roofing, and in containers for corrosive liquids. By the time of the Roman Empire, it was already in wide use in aqueducts and public water systems, as well as in cooking and storage utensils. Its alloys are used as solder, type metal, and various antifriction materials. The metal and the dioxide are used in storage batteries, and much metal is used in cable covering, plumbing and ammunition. Because of its high nuclear cross section, lead is extensively used as a radiation shield around X-ray equipment and nuclear reactors.

3.2 ELEMENTAL LEAD

In comparison with the most abundant metals in the earth's crust (aluminum and iron), lead is a rare metal; even copper and zinc are more abundant by factors of five and eight, respectively. Lead is, however, more abundant than the other toxic heavy metals; its abundance in the earth's crust has been estimated (Moeller, 1952) to be as high as 1.6×10^{-3} percent, although some other authors (Heslop and Jones, 1976) suggest a lower value of 2×10^{-4} percent. Either of these estimates suggests that the abundance of lead is more than 100 times that of cadmium or mercury, two other significant systemic metallic poisons. More important, since lead occurs in highly concentrated ores from which it is readily separated, the availability of lead is far greater than its natural abundance would suggest. The great environmental significance of lead is the result both of its utility and of its availability. Lead ranks fifth among metals in tonnage consumed, after iron, copper, aluminum and zinc; it is, therefore, produced in far larger quantities than any other toxic heavy metal (Dyrssen, 1972). The properties of elemental lead are summarized in Table 3-1.

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the tetravalent (+4) oxidation state. This important chemical feature is a direct result of the fact that the strengths of single bonds between the Group IV atoms and other atoms generally decrease as the atomic number of the Group IV atom increases (Cotton and Wilkinson, 1980). Thus, the average energy of a C-H bond is 100 kcal/mole, and it is this factor that stabilizes CH_4 relative to CH_2; for lead, the Pb-H energy is only approximately 50 kcal/mole (Shaw and Allred, 1970), and this is presumably too small to compensate for the Pb(II) → Pb(IV) promotional energy. It is this same feature that explains the marked difference in the tendencies to catenation shown by these elements. Though C-C bonds are present in literally millions of compounds, for lead catenation occurs only in organolead compounds. Lead does, however, form compounds like Na_4Pb_9 which contain distinct polyatomic lead clusters (Britton, 1964), and Pb-Pb bonds are found in the cationic cluster $[Pb_6O(OH)_8]^{+4}$ (Olin and Soderquist, 1972).

A listing of the solubilities and physical properties of the more common compounds of lead is given in Appendix 3A. As can be discerned from those data, most inorganic lead salts are sparingly soluble (e.g., PbF_2, $PbCl_2$) or virtually insoluble ($PbSO_4$, $PbCrO_4$) in water; the notable exceptions are lead nitrate, $Pb(NO_3)_2$, and lead acetate, $Pb(OCOCH_3)_2$. Inorganic lead (II) salts are, for the most part, relatively high-melting-point solids with correspondingly low vapor pressures at room temperatures. The vapor pressures of the most commonly encountered lead salts are also tabulated in Appendix 3A. The transformation of lead salts in the atmosphere is discussed in Chapter 6.

3.4 ORGANOMETALLIC CHEMISTRY OF LEAD

The properties of organolead compounds (i.e., compounds containing bonds between lead and carbon) are entirely different from those of the inorganic compounds of lead; although a few organolead(II) compounds, such as dicyclopentadienyllead, $Pb(C_5H_5)_2$, are known, the organic chemistry of lead is dominated by the tetravalent (+4) oxidation state. An important property of most organolead compounds is that they undergo photolysis when exposed to light (Rufman and Rotenberg, 1980).

Because of their use as antiknock agents in gasoline and other fuels, the most important organolead compounds have been the tetraalkyl compounds tetraethyllead (TEL) and tetramethyllead (TML). As would be expected for such nonpolar compounds, TEL and TML are insoluble in water but soluble in hydrocarbon solvents (e.g., gasoline). These two compounds are manufactured by the reaction of the alkyl chloride with lead-sodium alloy (Shapiro and Frey, 1968):

$$4NaPb + 4C_2H_5Cl \rightarrow (C_2H_5)_4Pb + 3Pb + 4NaCl \qquad (3\text{-}1)$$

Table 3A-1. (continued). PHYSICAL PROPERTIES OF INORGANIC LEAD COMPOUNDS[1]

Compound	Formula	M.W.	S.G.	M.P.	Solubility, g/100 ml: Cold water	Hot water	Other solvents
Nitrate, basic	$Pb(OH)NO_3$	286.20	5.93	d180	19.4	s	sa
Oxalate	PbC_2O_4	295.21	5.28	d300	0.00016		sa
Oxide	PbO	223.19	9.53	888	0.0017		s,alk
Dioxide	PbO_2	239.19	9.375	d290	i	i	sa
Oxide (red)	Pb_3O_4	685.57	9.1	d500	i	i	sa
Phosphate	$Pb_3(PO_4)_2$	811.51	7	1014	$1.4x10^{-5}$	i	s,alk
Sulfate	$PbSO_4$	303.25	6.2	1170	0.00425	0.0056	
Sulfide	PbS	239.25	7.5	1114	$8.6x10^{-5}$		sa
Sulfite	$PbSO_3$	287.25		d	i	i	sa
Thiocyanate	$Pb(SCN)_2$	323.35	3.82	d190	0.05	0.2	s,alk

Abbreviations: a - acid; al - alcohol; alk - alkali; d - decomposes; expl - explodes; glyc - glycol; i - insoluble; s - soluble; M.W. - molecular weight; S.G. - specific gravity; and M.P. - melting point.

Source: Weast, 1975.

for bond formation. In general, the metal atom occupies a central position in the complex, as exemplified by the lead atom in tetramethyllead (Figure 3-1a) which is tetrahedrally surrounded by four methyl groups. In these simple organolead compounds, the lead is usually present as Pb(IV), and the complexes are relatively inert. These simple ligands, which bind to metal at only a single site, are called monodentate ligands. Some ligands, however, can bind to the metal atom by more than one donor atom, so as to form a heterocyclic ring structure. Rings of this general type are called chelate rings, and the donor molecules which form them are called polydentate ligands or chelating agents. In the chemistry of lead, chelation normally involves Pb(II), leading to kinetically quite labile (although thermodynamically stable) octahedral complexes. A wide variety of biologically significant chelates with ligands, such as amino acids, peptides, nucleotides and similar macromolecules, are known. The simplest structure of this type occurs with the amino acid glycine, as represented in Figure 3-1b for a 1:2 (metal:ligand) complex. The importance of chelating agents in the present context is their widespread use in the treatment of lead and other metal poisoning.

Metals are often classified according to some combination of their electronegativity, ionic radius and formal charge (Ahrland, 1966, 1968, 1973; Basolo and Pearson, 1967; Nieboer and Richardson, 1980; Pearson, 1963, 1968). These parameters are used to construct empirical classification schemes of relative hardness or softness. In these schemes, "hard" metals form strong bonds with "hard" anions and likewise "soft" metals with "soft" anions. Some metals are borderline, having both soft and hard character. Pb(II), although borderline, demonstrates primarily soft character (Figure 3-2). The terms Class A may also be used to refer to hard metals, and Class B to soft metals. Since Pb(II) is a relatively soft (or class B) metal ion, it forms strong bonds to soft donor atoms like the sulfur atoms in the cysteine residues of proteins and enzymes; it also coordinates strongly with the imidazole groups of histidine residues and with the carboxyl groups of glutamic and aspartic acid residues. In living systems, therefore, lead atoms bind to these peptide residues in proteins, thereby preventing the proteins from carrying out their functions by changing the tertiary structure of the protein or by blocking the substrate's approach to the active site of the protein. As has been demonstrated in several studies (Jones and Vaughn, 1978; Williams and Turner, 1981; Williams et al., 1982), there is an inverse correlation between the LD_{50} values of metal complexes and the chemical softness parameter (σp) (Pearson and Mawby, 1967). Thus, for both mice and Drosophila, soft metal ions like lead(II) have been found to be more toxic than hard metal ions (Williams et al., 1982). This classification of metal ions according to their toxicity has been discussed in detail by Nieboer and Richardson (1980). Lead(II) has a higher softness parameter than either cadmium(II) or mercury(II), so lead(II) compounds would not be expected to be as toxic as their cadmium or mercury analogues.

For a given metal, M, and two ligands, B and B-B, which are chemically similar, it is established that k_1 and k_a have similar values to each other, as do k_2 and k_b and k_4 and k_d; each of these pairs of terms represents chemically similar processes. The origin of the chelate effect lies in the very large value of k_3 relative to that of k_c. This comes about because k_3 represents a unimolecular process, whereas k_c is a bimolecular rate constant. Consequently, $K_2 >> K_1$.

This concept can, of course, be extended to polydentate ligands; in general, the more extensive the chelation, the more stable the metal complex. Hence, one would anticipate, correctly, that polydentate chelating agents such as penicillamine or EDTA can form extremely stable complexes with metal ions.

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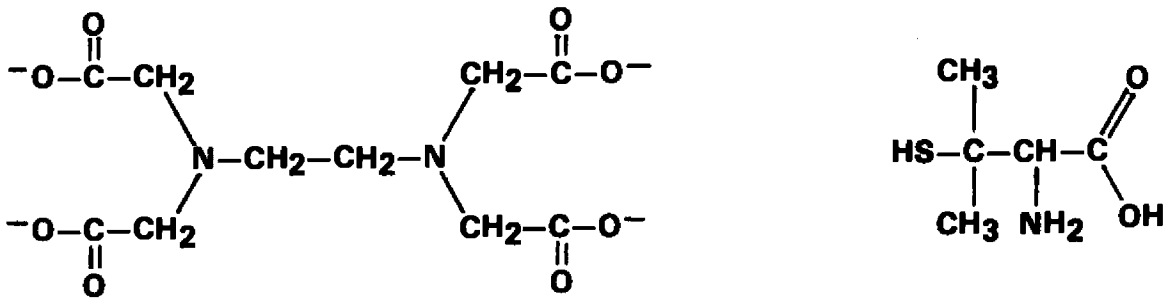

Figure 3-3. Structure of chelating agents.

The role of the chelating agents is to compete with the peptides for the metal by forming stable chelate complexes that can be transported from the protein and eventually be exreted by the body. For simple thermodynamic reasons (see Appendix 3A), chelate complexes are much more stable than monodentate metal complexes, and it is this enhanced stability that is the basis for their ability to compete favorably with proteins and other ligands for the metal ions. The chelating agents most commonly used for the treatment of lead poisoning are ethylenediaminetetraacetate ions (EDTA), D-penicillamine (Figure 3-3) and their derivatives. EDTA is known to act as a hexadentate ligand toward metals (Lis, 1978; McCandlish et al., 1978). X-ray diffraction studies have demonstrated that D-penicillamine is a tridentate ligand binding through its sulfur, nitrogen and oxygen atoms to cobalt (de Meester and Hodgson, 1977a; Helis; et al., 1977), chromium (de Meester and Hodgson, 1977b), cadmium (Freeman et al., 1976), and lead itself (Freeman et al., 1974), but both penicillamine and other cysteine derivatives may act as bidentate ligands (Carty and Taylor, 1977; de Meester and Hodgson, 1977c). Moreover, penicillamine binds to mercury only through its sulfur atoms (Wong et al., 1973; Carty and Taylor, 1976).

It should be noted that both the stoichiometry and structures of metal chelates depend upon pH, and that structures different from those manifest in solution may occur in crystals. It will suffice to state, however, that several ligands can be found that are capable of sufficiently strong chelation with lead present in the body under physiological conditions to permit their use in the effective treatment of lead poisoning.

4.2 SAMPLING

The purpose of sampling is to determine the nature and concentration of lead in the environment. Sampling strategy is dictated by research needs. This strategy encompasses site selection, choice of instrument used to obtain representative samples, and choice of method used to preserve sample integrity. In the United States, sampling stations for air pollutants have been operated since the early 1950's. These early stations were a part of the National Air Surveillance Network (NASN), which has now become the National Filter Analysis Network (NFAN). Two other types of networks have been established to meet specific data requirements. State and Local Air Monitoring Stations (SLAMS) provide data from specific areas where pollutant concentrations and population densities are the greatest and where monitoring of compliance to standards is critical. The National Air Monitoring Station (NAMS) network is designed to serve national monitoring needs, including assessment of national ambient trends. SLAMS and NAMS stations are maintained by state and local agencies and the air samples are analyzed in their laboratories. Stations in the NFAN network are maintained by state and local agencies, but the samples are analyzed by laboratories in the U.S. Environmental Protection Agency, where quality control procedures are rigorously maintained.

Data from all three networks are combined into one data base, the National Aerometric Data Bank (NADB). These data may be individual chemical analyses of a 24-hour sampling period arithmetically averaged over a calendar period, or chemical composites of several filters used to determine a quarterly composite. Data are occasionally not available because they do not conform to strict statistical requirements. A summary of the data from the NADB appears in Section 7.2.1.

4.2.1 Regulatory Siting Criteria for Ambient Aerosol Samplers

In September of 1981, EPA promulgated regulations establishing ambient air monitoring and data reporting requirements for lead [C.F.R. (1982) 40:§58] comparable to those already established in May of 1979 for the other criteria pollutants. Whereas sampling for lead is accomplished when sampling for TSP, the designs of lead and TSP monitoring stations must be complementary to insure compliance with the NAMS criteria for each pollutant, as presented in Table 4-1, Table 4-2, and Figure 4-1.

In general, the criteria with respect to monitoring stations designate that there must be at least two SLAMS sites for lead in any area which has a population greater than 500,000 and/or any area where lead concentration currently exceeds the ambient lead standard (1.5 $\mu g/m^3$) or has exceeded it since January 1, 1974. In such areas, the SLAMS sites designated as part of the NAMS network must include a microscale or middlescale site located near a major roadway (≥30,000 ADT), as well as a neighborhood scale site located in a highly populated residential sector with high traffic density (≥30,000 ADT).

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TABLE 4-2. TSP NAMS CRITERIA

Approximate Number of Stations Per Area			
		Concentration	
Population Category	High[1]	Medium[2]	Low[3]
High -- >500,000	6-8	4-6	0-2
Medium -- 100-500,000	4-6	2-4	0-2
Low -- 50-100,000	2-4	1-2	0

[1]When TSP Concentration exceeds by 20% Primary Ambient Air Standard of 75 $\mu g/m^3$ annual geometric mean.

[2]TSP Concentration > Secondary Ambient Air Standard of 60 $\mu g/m^3$ annual geometric mean.

[3]TSP Concentration < Secondary Ambient Air Standard.

Source: C.F.R. (1982) 40:§58 App D

With respect to the siting of monitors for lead and other criteria pollutants, there are standards for elevation of the monitors above ground level, setback from roadways, and setback from obstacles. A summary of the specific siting requirements for lead is presented in Table 4-1 and summarized below:

- Samples must be placed between 2 and 15 meters from the ground and greater than 20 meters from trees.
- Spacing of samplers from roads should vary with traffic volume; a range of 5 to 100 meters from the roadway is suggested.
- Distance from samplers to obstacles must be at least twice the height the obstacle protrudes above the sampler.
- There must be a 270° arc of unrestricted air flow around the monitor to include the prevailing wind direction that provides the maximum pollutant concentration to the monitor.
- No furnaces or incineration flues should be in close proximity to the monitor.

APPENDIX 3A

PHYSICAL/CHEMICAL DATA FOR LEAD COMPOUNDS

3A.1 DATA TABLES

Table 3A-1. PHYSICAL PROPERTIES OF INORGANIC LEAD COMPOUNDS[1]

Compound	Formula	M.W.	S.G.	M.P.	Solubility, g/100 ml		
					Cold water	Hot water	Other solvents
Lead	Pb	207.19	11.35	327.5	i	i	sa
Acetate	$Pb(C_2H_3O_2)_2$	325.28	3.25	280	44.3	221^{50}	s glyc
Azide	$Pb(N_3)_2$	291.23	-	expl.	0.023	0.09^{70}	-
Bromate	$Pb(BrO_3)_2 \cdot H_2O$	481.02	5.53	d180	1.38	sl s	-
Bromide	$PbBr_2$	367.01	6.66	373	0.8441	4.71^{100}	sa
Carbonate	$PbCO_3$	267.20	6.6	d315	0.00011	d	sa,alk
Carbonate, basic	$2PbCO_3 \cdot Pb(OH)_2$	775.60	6.14	d400	i	i	s HNO_3
Chloride	$PbCl_2$	278.10	5.85	501	0.99	3.34^{100}	i al
Chlorobromide	PbClBr	322.56					
Chromate	$PbCrO_4$	323.18	6.12	844	$6x10^{-6}$	i	sa,alk
Chromate, basic	$PbCrO_4 \cdot PbO$	546.37	6.63		i	i	sa,alk
Cyanide	$Pb(CN)_2$	259.23			sl s	s	s KCN
Fluoride	PbF_2	245.19	8.24	855	0.064		s HNO_3
Fluorochloride	PbFCl	261.64	7.05	601	0.037	0.1081	
Formate	$Pb(CHO_2)_2$	297.23	4.63	d190	1.6	20	i al
Hydride	PbH_2	209.21		d			
Hydroxide	$Pb(OH)_2$	241.20		d145	0.0155	sl s	sa,alk
Iodate	$Pb(IO_3)_2$	557.00	6.155	d300	0.0012	0.003	s HNO_3
Iodide	PbI_2	461.00	6.16	402	0.063	0.41	s,alk
Nitrate	$Pb(NO_3)_2$	331.20	4.53	d470	37.65	127	s,alk

To clarify the relationship between monitoring objectives and the actual siting of a monitor, the concept of a spatial scale of representativeness was developed. The spatial scales are described in terms of the physical dimensions of the air space surrounding the monitor throughout which pollutant concentrations are fairly similar. Table 4-3 describes the scales of representativeness while Table 4-4 relates monitoring objectives to the appropriate spatial scale.

The time scale may also be an important factor. A study by Lynam (1972) illustrates the effect of setback distance on short-term (15 minute) measurements of lead concentrations directly downwind from the source. They found sharp reductions in lead concentration with increasing distance from the roadway. A similar study by PEDCo Environmental, Inc. (1981) did not show the same pronounced reduction when the data were averaged over monthly or quarterly time periods. The apparent reason for this effect is that windspeed and direction are not consistent. Therefore, siting criteria must include sampling times sufficiently long to include average windspeed and direction, or a sufficient number of samples must be collected over short sampling periods to provide an average value consistent with a 24-hour exposure.

4.2.2 Ambient Sampling for Particulate and Gaseous Lead

Airborne lead is primarily inorganic particulate matter but may occur in the form of organic gases. Devices used for collecting samples of ambient atmospheric lead include the standard hi-vol and a variety of other collectors employing filters, impactors, impingers, or scrubbers, either separately or in combination. Some samplers measure total particulate matter gravimetrically; thus the lead data are usually expressed in μg/g PM or $\mu g/m^3$ air. Other samplers do not measure PM gravimetrically; therefore, the lead data can only be expressed as $\mu g/m^3$. Some samplers measure lead deposition expressed in $\mu g/cm^2$. Some instruments separate particles by size. As a general rule, particles smaller than 2.5 μm are defined as fine, and those larger than 2.5 μm are defined as coarse.

In a typical sampler, the ambient air is drawn down into the inlet and deposited on the collection surface after one or more stages of particle size separation. Inlet effectiveness, internal wall losses, and retention efficiency of the collection surface may bias the collected sample by selectively excluding particles of certain sizes.

4.2.2.1 High Volume Sampler (hi-vol). The present SLAMS and NAMS employ the standard hi-vol sampler (Robson and Foster, 1962; Silverman and Viles, 1948; U.S. Environmental Protection Agency, 1971) as part of their sampling networks. As a Federal Reference Method Sampler, the hi-vol operates with a specific flow rate range of 1.13 to 1.70 m^3/min, drawing air through a

Table 3A-2. TEMPERATURE VARIATION OF THE VAPOR PRESSURES OF COMMON LEAD COMPOUNDS

Name	Formula	M.P.	Temperature °C					
			1 mm	10 mm	40 mm	100 mm	400 mm	760 mm
Lead	Pb	327.4	973	1162	1309	1421	1630	1744
Lead bromide	$PbBr_2$	373	513	610	686	745	856	914
Lead chloride	$PbCl_2$	501	547	648	725	784	893	954
Lead flouride	PbF_2	855	solid	904	1003	1080	1219	1293
Lead iodide	PbI_2	402	479	571	644	701	807	872
Lead oxide	PbO	890	943	1085	1189	1265	1402	1472
Lead sulfide	PbS	1114	852 (solid)	975 (solid)	1048 (solid)	1108 (solid)	1221	1281

Source: Stull, 1947

3A.2. THE CHELATE EFFECT

The stability constants of chelated complexes are normally several orders of magnitude higher than those of comparable monodentate complexes; this effect is called the chelate effect, and is very readily explained in terms of kinetic considerations. A comparison of the binding of a single bidentate ligand with that of two molecules of a chemically similar monodentate ligand shows that, for the monodentate case, the process can be represented by the equations:

$$M + B \underset{k_b}{\overset{k_a}{\rightleftharpoons}} M\text{-}B \qquad (3A\text{-}1)$$

$$M\text{-}B + B \underset{k_d}{\overset{k_c}{\rightleftharpoons}} MB_2 \qquad (3A\text{-}2)$$

The related expressions for the bidentate case are:

$$M + B\text{-}B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} M\text{-}B\text{-}B \qquad (3A\text{-}3)$$

$$M\text{-}B\text{-}B \underset{k^4}{\overset{k_3}{\rightleftharpoons}} M \begin{matrix} B \\ B \end{matrix} \qquad (3A\text{-}4)$$

The overall equilibrium constants, therefore, are:

$$K^1 = \frac{k_a k_c}{k_b k_d}; \qquad K_2 = \frac{k_1 k_3}{k_2 k_4}$$

200 x 250 mm glass fiber filter. At these flow rates, 1600 to 2500 m^3 of air per day are sampled. Many hi-vol systems are presently equipped with mass flow sensors to control the total flow rate through the filter.

The present hi-vol approach has been shown, during performance characterization tests, to have a number of deficiencies. First, wind tunnel testing by Wedding et al. (1977) has shown that the inlet characteristics of the hi-vol sampler are strongly affected by particle size, windspeed, and wind direction. However, since most lead particles have been shown to have a mass median diameter (MMD) in the range of 0.25 to 1.4 μm (Lee and Goranson, 1972), the hi-vol sampler should present reasonably good estimates of ambient lead concentrations. However, for particles greater than 5 μm, the hi-vol system is unlikely to collect representative samples (McFarland and Rodes, 1979; Wedding et al., 1977). In addition, Lee and Wagman (1966) and Stevens et al. (1978) have documented that the use of glass fiber filters leads to the formation of artifactual sulfate. Spicer et al. (1978) suggested a positive artifactual nitrate, while Stevens et al. (1980) showed both a positive and negative artifact may occur with glass or quartz filters when using a hi-vol sampler.

4.2.2.2 Dichotomous Sampler. The dichotomous sampler collects two particle size fractions, typically 0 to 2.5 μm and 2.5 μm to the upper cutoff of the inlet employed (normally 10 μm). The impetus for the dichotomy of collection, which approximately separates the fine and coarse particles, was provided by Whitby et al. (1972) to assist in the identification of particle sources. A 2.5 μm cutpoint for the separator was also recommended by Miller et al. (1979) because it satisfied the requirements of health researchers interested in respirable particles, provided adequate separation between two naturally occurring peaks in the size distribution, and was mechanically practical. Because the fine and coarse fractions collected in most locations tend to be acidic and basic, respectively, this separation also minimizes potential particle interaction after collection.

The particle separation principle used by this sampler was described by Hounam and Sherwood (1965) and Conner (1966). The version now in use by EPA was developed by Loo et al. (1979). The separation principle involves acceleration of the particles through a nozzle. Ninety percent of the flowstream is diverted to a small particle collector, while the larger particles continue by inertia toward the large particle collection surface. The inertial virtual impactor design causes 10 percent of the fine particles to be collected with the coarse particle fraction. Therefore, the mass of fine and coarse particles must be adjusted to allow for their cross contamination. This mass correction procedure has been described by Dzubay et al. (1982).

4. SAMPLING AND ANALYTICAL METHODS FOR ENVIRONMENTAL LEAD

4.1 INTRODUCTION

Lead, like all criteria pollutants, has a designated Reference Method for monitoring and analysis as required in State Implementation Plans for determining compliance with the lead National Ambient Air Quality Standard. The Reference Method [C.F.R. (1982) 40:§50] uses a high volume sampler (hi-vol) for sample collection and atomic absorption spectrometry for analysis. The reference method may be revised to require collection of a specific size fraction of atmospheric particles. Size specific inlets will be discussed in Section 4.2.3.

Airborne lead originates principally from man-made sources, about 75 to 90 percent from automobile exhaust, and is transported through the atmosphere to vegetation, soil, water, and animals. Knowledge of environmental concentrations of lead and the extent of its movement among various media is essential to control lead pollution and to assess its effects on human populations.

The collection and analysis of environmental samples for lead require a rigorous quality assurance program [C.F.R. (1982) 40:§58]. It is essential that the investigator recognize all sources of contamination and use every precaution to eliminate them. Contamination occurs on the surfaces of collection containers and devices, on the hands and clothing of the investigator, in the chemical reagents, in the laboratory atmosphere, and on the labware and tools used to prepare the sample for analysis. General procedures for controlling contamination in trace metal analysis are described by Zief and Mitchell (1976). Specific details for the analysis of lead are given in Patterson and Settle (1976). In the following discussion of methods for sampling and analysis, it is assumed that all procedures are normally carried out with precise attention to contamination control.

In the following sections, the specific operation, procedure and instrumentation involved in monitoring and analyzing environmental lead are discussed. Site selection criteria are treated briefly due to the lack of verifying data. Much remains to be done in establishing valid criteria for sampler location. The various types of samples and substrates used to collect airborne lead are described. Methods for collecting dry deposition, wet deposition, aqueous, soil and vegetation samples are also reviewed along with current sampling methods specific to mobile and stationary sources. Finally, advantages and limitations of techniques for sample preparation and analysis are discussed.

Cascade impactors typically have 2 to 10 stages, and flowrates for commercial low-volume versions range from about 0.01 to 0.10 m^3/min. Lee and Goranson (1972) modified a commercially available 0.03 m^3/min low-volume impactor and operated it at 0.14 m^3/min to obtain larger mass collections on each stage. Cascade impactors have also been designed to mount on a hi-vol sampler and operate at flowrates as high as 0.6 to 1.1 m^3/min.

Particle size cutpoints for each stage depend primarily on sampler geometry and flowrate. The smallest particle size cutpoint routinely used is approximately 0.3 μm, although special low-pressure impactors such as that described by Hering et al. (1978) are available with cutpoints as small as 0.05 μm. However, due to the low pressure, volatile organics and nitrates are lost during sampling. A membrane filter is typically used after the last stage to collect the remaining small particles.

4.2.2.4 Dry Deposition Sampling. Dry deposition may be measured directly with surrogate or natural surfaces, or indirectly using micrometeorological techniques. The earliest surrogate surfaces were dustfall buckets placed upright and exposed for several days. The HASL wet-dry collector is a modification which permits one of a pair of buckets to remain covered except during rainfall. These buckets do not collect a representative sample of particles in the small size range where lead is found because the rim perturbs the natural turbulent flow of the main airstream (Hicks et al., 1980). They are widely used for other pollutants, especially large particles, in the National Atmospheric Deposition Program.

Other surrogate surface devices with smaller rims or no rims have been developed recently (Elias et al., 1976; Lindberg et al., 1979; Peirson et al., 1973). Peirson et al. (1973) used horizontal sheets of filter paper exposed for several days with protection from rainfall. Elias et al. (1976) used Teflon® disks held rigid with a 1 cm Teflon® ring. Lindberg et al. (1979) used petri dishes suspended in a forest canopy. In all of these studies, the calculated deposition velocity (see Section 6.3.1) was within the range expected for small aerosol particles.

A few studies have measured direct deposition on vegetation surfaces using chemical washing techniques to remove surface particles. These determinations are generally 4 to 10 times lower than comparable surrogate surface measurements (Elias et al., 1976; Lindberg et al., 1979), but the reason for this difference could be that natural surfaces represent net accumulation rather than total deposition. Lead removed by rain or other processes would show an apparently lower deposition rate.

There are several micrometeorological techniques that have been used to measure particle deposition. They overcome the major deficiency of surrogate surfaces, the lack of correlation between the natural and artificial surfaces, but micrometeorological techniques require expensive equipment and skilled operators. They measure instantaneous or short-term deposition

TABLE 4-1. DESIGN OF NATIONAL AIR MONITORING STATIONS

Criteria	TSP (Final Rule)	Air Pb (Final Rule)				
Stations required						
Spatial scale						
Category (a)	Neighborhood scale	Microscale or middle scale				
Category (b)	-	Neighborhood scale				
Number required	As per Table 4-2	Minimum 1 each category where population >500,000				
Siting						
Category (a)	High traffic and population density neighborhood scale	Major roadway microscale	or	Major roadway middle scale		
	>3000	≥30,000		≥10,000	20,000	≥40,000
Meters from edge of roadway	As per Figure 4-1	5-15		>15-50	>15-75	>15-100
meters above ground level	2-15	2-7		2-15	2-15	2-15
Category (b)		High traffic and population density neighborhood scale				
		≤10,000	20,000	≥40,000		
Meters from edge of roadway		>50	>75	>100		
Meters above ground level		2-15	2-15	2-15		

Source: C.F.R. (1982) 40:§58 App E

directly in the stack or exhaust stream. In the tentative ASTM method for sampling for atmospheric lead, air is pulled through a 0.45 μm membrane filter and an activated carbon adsorption tube (American Society for Testing and Materials, 1975a). In a study of manual methods for measuring emission concentrations of lead and other toxic materials, Coulson et al. (1973), recommended use of a filter, a system of impingers, a metering system, and a pump.

4.2.3.2 Mobile Sources. Three principal procedures have been used to obtain samples of auto exhaust aerosols for subsequent analysis for lead compounds: a horizontal dilution tunnel, plastic sample collection bags and a low residence time proportional sampler. In each procedure, samples are air diluted to simulate roadside exposure conditions. In the most commonly used procedure, a large horizontal air dilution tube segregates fine combustion-derived particles from larger lead particles ablated from combustion chamber and exhaust deposits. In this procedure, hot exhaust is ducted into a 56-cm diameter, 12-m long, air dilution tunnel and mixed with filtered ambient air in a 10-cm diameter mixing baffle in a concurrent flow arrangement. Total exhaust and dilution airflow rate is 28 to 36 m^3/min, which produces a residence time of approximately 5 sec in the tunnel. At the downstream end of the tunnel, samples of the aerosol are obtained by means of isokinetic probes using filters or cascade impactors (Habibi, 1970).

In recent years, various configurations of the horizontal air dilution tunnel have been developed. Several dilution tunnels have been made of polyvinyl chloride with a diameter of 46 cm, but these are subject to wall losses due to charge effects (Gentel et al., 1973; Moran et al., 1972; Trayser et al., 1975). Such tunnels of varying lengths have been limited by exhaust temperatures to total flows above approximately 11 m^3/min. Similar tunnels have a centrifugal fan located upstream, rather than a positive displacement pump located downstream (Trayser et al., 1975). This geometry produces a slight positive pressure in the tunnel and expedites transfer of the aerosol to holding chambers for studies of aerosol growth. However, turbulence from the fan may affect the sampling efficiency. Since the total exhaust plus dilution airflow is not held constant in this system, potential errors can be reduced by maintaining a very high dilution air/exhaust flow ratio (Trayser et al., 1975).

There have also been a number of studies using total filtration of the exhaust stream to arrive at material balances for lead with rather low back-pressure metal filters in an air distribution tunnel (Habibi, 1973; Hirschler et al., 1957; Hirschler and Gilbert, 1964; Sampson and Springer, 1973). The cylindrical filtration unit used in these studies is better than 99 percent efficient in retaining lead particles (Habibi, 1973). Supporting data for lead balances generally confirm this conclusion (Kunz et al., 1975).

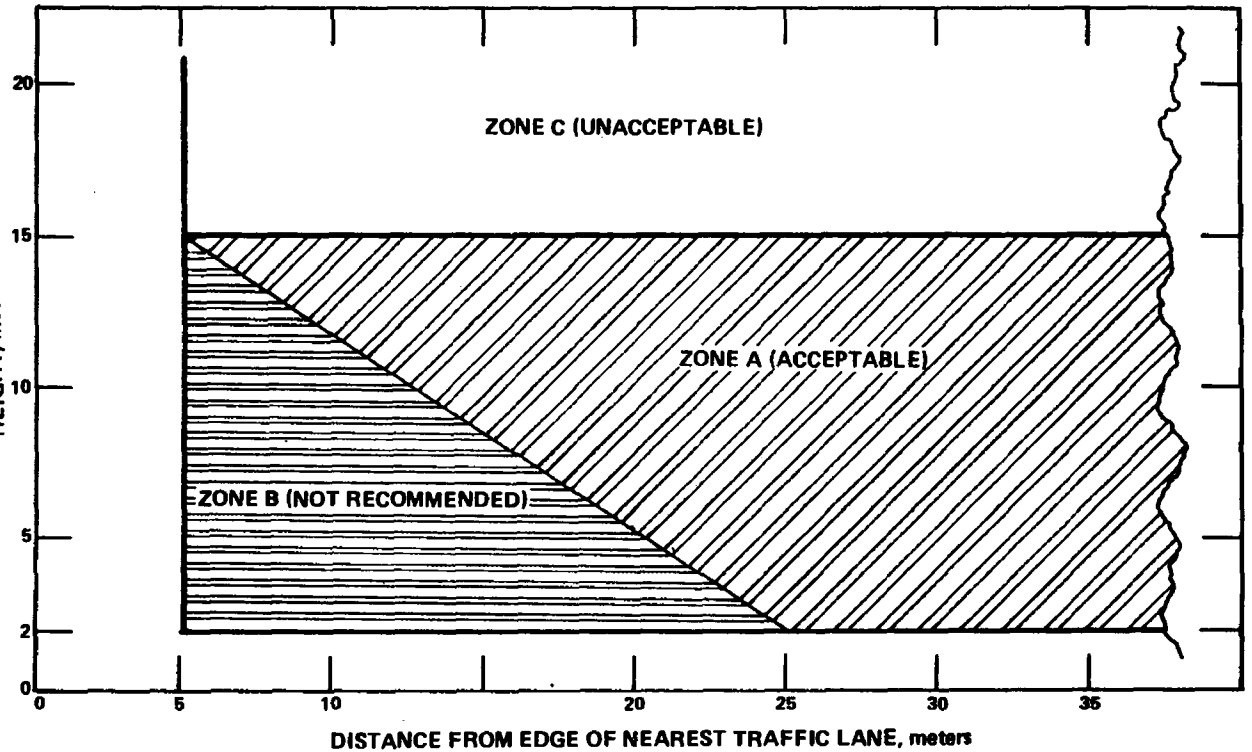

Figure 4-1. Acceptable zone for siting TSP monitors where the average daily traffic exceeds 3000 vehicles/day.

Zone A: Recommended for neighborhood, urban, regional and most middle spatial scales. All NAMS are in this zone.
Zone B: If SLAMS are placed in Zone B they have middle scale of representativeness.

Source: 46 FR 44159-44172

4.2.4.2 Surface Water. Atmospheric lead may be dissolved in water as hydrated ions, chemical complexes, and soluble compounds, or it may be associated with suspended matter. Because the physicochemical form often influences environmental effects, there is a need to differentiate among the various chemical forms of lead. Complete differentiation among all such forms is a complex task that has not yet been fully accomplished. The most commonly used approach is to distinguish between dissolved and suspended forms of lead. All lead passing through a 0.45 μm membrane filter is operationally defined as dissolved, while that retained on the filter is defined as suspended (Kopp and McKee, 1979).

When sampling water bodies, flow dynamics should be considered in the context of the purpose for which the sample is collected. Water at the convergence point of two flowing streams, for example, may not be well mixed for several hundred meters. Similarly, the heavy metal concentrations above and below the thermocline of a lake may be very different. Thus, several samples should be selected in order to define the degree of horizontal or vertical variation. The final sampling plan should be based on the results of pilot studies. In cases where the average concentration is of primary concern, samples can be collected at several points and then mixed to obtain a composite.

Containers used for sample collection and storage should be fabricated from essentially lead-free plastic or glass, e.g., conventional polyethylene, Teflon®, or quartz. These containers must be leached with hot acid for several days to ensure minimum lead contamination (Patterson and Settle, 1976). If only the total lead is to be determined, the sample may be collected without filtration in the field. Nitric acid should be added immediately to reduce the pH to less than 2 (U.S. Environmental Protection Agency, 1978). The acid will normally dissolve the suspended lead. Otherwise, it is recommended that the sample be filtered upon collection to separate the suspended and dissolved lead and the latter preserved by acid addition as above. It is also recommended that water samples be stored at 4°C until analysis to avoid further leaching from the container wall (Fishman and Erdmann, 1973; Kopp and Kroner, 1967; Lovering, 1976; National Academy of Sciences, 1972; U.S. Environmental Protection Agency, 1978).

4.2.4.3 Soils. The distance and depth gradients associated with lead in soil from emission sources must be considered in designing the sampling plan. Beyond that, actual sampling is not particularly complex (Skogerboe et al., 1977b). Vegetation, litter, and large objects such as stones should not be included in the sample. Depth samples should be collected at 2 cm intervals to preserve vertical integrity. The samples should be air dried and stored in sealed containers until analyzed.

TABLE 4-3. DESCRIPTION OF SPATIAL SCALES OF REPRESENTATIVENESS

Microscale	Defines ambient concentrations in air volumes associated with areas ranging from several to 100 meters in size.
Middle Scale	Defines concentrations in areas from 100 to 500 meters (area up to several city blocks).
Neighborhood Scale	Defines concentrations in an extended area of uniform land use, within a city, from 0.5 to 4.0 kilometers in size.
Urban Scale	Defines citywide concentrations, areas from 4-50 kilometers in size. Usually requires more than one site.
Regional Scale	Defines concentrations in a rural area with homogeneous geography. Range of tens to hundreds of kilometers.
National and Global Scales	Defines concentrations characterizing the U.S. and the globe as a whole.

Source: C.F.R. (1982) 40:§58 App. D

TABLE 4-4. RELATIONSHIP BETWEEN MONITORING OBJECTIVES AND APPROPRIATE SPATIAL SCALES

Monitoring objective	Appropriate spatial scale for siting air monitors
Highest Concentration	Micro, Middle, Neighborhood (sometimes Urban).
Population	Neighborhood, Urban
Source Impact	Micro, Middle, Neighborhood
General (Background)	Neighborhood, Regional

Source: C.F.R. (1982) 40:§58 App. D

sample collected is large, then the effects of these trace contaminants may be negligible (Witz and MacPhee, 1976). Procedures for cleaning filters to reduce the lead blank rely on washing with acids or complexing agents (Gandrud and Lazrus, 1972). The type of filter and the analytical method to be used often determines the ashing technique. In some methods, e.g., X-ray fluorescence, analysis can be performed directly on the filter if the filter material is suitable (Dzubay and Stevens, 1975). Skogerboe (1974) provided a general review of filter materials.

The main advantages of glass fiber filters are low pressure drop and high particle collection efficiency at high flow rates. The main disadvantage is variable lead blank, which makes their use inadvisable in many cases (Kometani et al., 1972; Luke at al., 1972). This has placed a high priority on the standardization of a suitable filter for hi-vol samples (Witz and MacPhee, 1976). Other investigations have indicated, however, that glass fiber filters are now available that do not present a lead interference problem (Scott et al., 1976b). Teflon® filters have been used since 1975 by Dzubay et al. (1982) and Stevens et al. (1978), who have shown these filters to have very low lead blanks (<2 ng/cm^2). The collection efficiencies of filters, and also of impactors, have been shown to be dominant factors in the quality of the derived data (Skogerboe et al., 1977a).

Sample preparation usually involves conversion to a solution through wet ashing of solids with acids or through dry ashing in a furnace followed by acid treatment. Either approach works effectively if used properly (Kometani et al., 1972; Skogerboe et al., 1977b). In one investigation of porous plastic Nuclepore® filters, some lead blanks were too high to allow measurements of ambient air lead concentrations (Skogerboe et al., 1977b).

4.3 ANALYSIS

The choice of analytical method depends on the nature of the data required, the type of sample being analyzed, the skill of the analyst, and the equipment available. For general determination of elemental lead, atomic absorption spectroscopy is widely used and recommended [40 C.F.R. (1982) 40:§50]. Optical emission spectrometry (Scott et al., 1976b) and X-ray fluorescence (Stevens et al., 1978) are rapid and inexpensive methods for multielemental analyses. X-ray fluorescence can measure lead concentrations reliably to 1 ng/m^3 using samples collected with commercial dichotomous samplers. Other analytical methods have specific advantages appropriate for special studies. Only those analytical techniques receiving widespread current use in lead analysis are described below. More complete reviews are available in the literature (American Public Health Association, 1971; Lovering, 1976; Skogerboe et al., 1977b; National Academy of Sciences, 1980).

Teflon® membrane filters with pore sizes as large as 2.0 μm can be used in the dichotomous sampler (Dzubay et al, 1982; Stevens et al., 1980) and have been shown to have essentially 100 percent collection efficiency for particles with an aerodynamic diameter as small as 0.03 μm (Liu et al., 1976; See Section 4.2.5). Because the sampler operates at a flowrate of 1 m^3/hr (167 l/min) and collects sub-milligram quantities of particles, a microbalance with a 1 μg resolution is recommended for filter weighing (Shaw, 1980). Removal of the fine particles via this fractionation technique may result in some of the collected coarse particles falling off the filter if care is not taken during filter handling and shipping. However, Dzubay and Barbour (1983) have developed a filter coating procedure which eliminates particle loss during transport. A study by Wedding et al. (1980) has shown that the Sierra® inlet to the dichotomous sampler was sensitive to windspeed. The 50 percent cutpoint (D_{50}) was found to vary from 10 to 22 μm over the windspeed range of 0 to 15 km/hr.

Automated versions of the sampler allow timely and unattended changes of the sampler filters. Depending on atmospheric concentrations, short-term samples of as little as 4 hours can provide diurnal pattern information. The mass collected during such short sample periods, however, is extremely small and highly variable results may be expected.

4.2.2.3 Impactor Samplers. Impactors provide a means of dividing an ambient particle sample into subfractions of specific particle size for possible use in determining size distribution. A jet of air is directed toward a collection surface, which is often coated with an adhesive or grease to reduce particle bounce. Large, high-inertia particles are unable to turn with the airstream and consequently hit the collection surface. Smaller particles follow the airstream and are directed toward the next impactor stage or to the filter. Use of multiple stages, each with a different particle size cutpoint, provides collection of particles in several size ranges.

For determining particle mass, removable impaction surfaces may be weighed before and after exposure. The particles collected may be removed and analyzed for individual elements. The selection and preparation of these impaction surfaces have significant effects on the impactor performance. Improperly coated or overloaded surfaces can cause particle bounce to lower stages resulting in substantial cutpoint shifts (Dzubay et al., 1976). Additionally, coatings may cause contamination of the sample. Marple and Willeke (1976) showed the effect of various impactor substrates on the sharpness of the stage cutpoint. Glass fiber substrates can also cause particle bounce or particle interception (Dzubay et al., 1976) and are subject to the formation of artifacts, due to reactive gases interacting with the glass fiber, similar to those on hi-vol sampler filters (Stevens et al., 1978).

Pachuta and Love (1980) collected particles on cellulose acetate filters. Disks (0.5 cm^2) were punched from these filters and analyzed by insertion of the nichrome cups containing the disks into a flame. Another application involves the use of graphite cups as particle filters with the subsequent analysis of the cups directly in the furnace system (Seeley and Skogerboe, 1974; Torsi et al., 1981). These two procedures offer the ability to determine particulate lead directly with minimal sample handling.

In an analysis using AAS and hi-vol samplers, atmospheric concentrations of lead were found to be 0.076 ng/m^3 at the South Pole (Maenhaut et al., 1979). Lead analyses of 995 particulate samples from the NASN were accomplished by AAS with an indicated precision of 11 percent (Scott et al., 1976a, see also Section 7.2.1.1). More specialized AAS methods for the determination of tetraalkyl lead compounds in water and fish tissue have been described by Chau et al. (1979) and in air by Birnie and Noden (1980) as well as Rohbock et al. (1980).

Atomic absorption requires as much care as other techniques to obtain highly precise data. Background absorption, chemical interference, background light loss, and other factors can cause errors. A major problem with AAS is that untrained operators use it in many laboratories without adequate quality control.

Techniques for AAS are still evolving. An alternative to the graphite furnace, evaluated by Jin and Taga (1982), uses a heated quartz tube through which the metal ion in gaseous hydride form flows continuously. Sensitivities were 1 to 3 ng/g for lead. The technique is similar to the hydride generators used for mercury, arsenic, and selenium. Other nonflame atomization systems, electrodeless discharge lamps, and other equipment refinements and technique developments have been reported (Horlick, 1982).

4.3.2 Emission Spectroscopy

Optical emission spectroscopy is based on the measurement of the light emitted by elements when they are excited in an appropriate energy medium. The technique has been used to determine the lead content of soils, rocks, and minerals at the 5 to 10 µg/g level with a relative standard deviation of 5 to 10 percent (Anonymous, 1963); this method has also been applied to the analysis of a large number of air samples (Scott et al., 1976b; Sugimae and Skogerboe, 1978). The primary advantage of this method is that it allows simultaneous measurement of a large number of elements in a small sample (Ward and Fishman, 1976).

In a study of environmental contamination by automotive lead, sampling times were shortened by using a sampling technique in which lead-free porous graphite was used both as the filter medium and as the electrode in the spectrometer (Copeland et al., 1973; Seeley and Skogerboe, 1974). Lead concentrations of 1 to 10 $µg/m^3$ were detected after a half-hour flow at 800 to 1200 ml/min through the filter.

only, and this deposition is inferred to be to a plane projected surface area only, not necessarily to vegetation surfaces.

Of the five micrometeorological techniques commonly used to measure particle deposition, only two have been used to measure lead particle deposition. Everett et al. (1979) used the profile gradient technique by which lead concentrations are measured at two or more levels within 10 m above the surface. Parallel meteorological data are used to calculate the net flux downward. Droppo (1980) used eddy correlation, which measures fluctuations in the vertical wind component with adjacent measurements of lead concentrations. The calculated differences of each can be used to determine the turbulent flux. These two micrometeorological techniques and the three not yet used for lead, modified Bowen, variance, and eddy accumulation, are described in detail in Hicks et al. (1980).

4.2.2.5 Gas Collection. When sampling ambient lead with systems employing filters, it is likely that vapor-phase organolead compounds will pass through the filter media. The use of bubblers downstream of the filter containing a suitable reagent or absorber for collection of these compounds has been shown to be effective (Purdue et al., 1973). Organolead may be collected on iodine crystals, adsorbed on activated charcoal, or absorbed in an iodine monochloride solution (Skogerboe et al., 1977b).

In one experiment, Purdue et al. (1973) operated two bubblers in series containing iodine monochloride solution. One hundred percent of the lead was recovered in the first bubbler. It should be noted, however, that the analytical detection sensitivity was poor. In general, use of bubblers limits the sample volume due to losses by evaporation and/or bubble carryover.

4.2.3 Source Sampling

Sources of lead include automobiles, smelters, coal-burning facilities, waste oil combustion, battery manufacturing plants, chemical processing plants, facilities for scrap processing, and welding and soldering operations (see Section 5.3.3). A potentially important secondary source is fugitive dust from mining operations and from soils contaminated with automotive emissions (Olson and Skogerboe, 1975). Chapter 5 contains a complete discussion of sources of lead emissions. The following sections discuss the sampling of stationary and mobile sources.

4.2.3.1 Stationary Sources. Sampling of stationary sources for lead requires the use of a sequence of samplers at the source of the effluent stream. Since lead in stack emissions may be present in a variety of physical and chemical forms, source sampling trains must be designed to trap and retain both gaseous and particulate lead. A sampling probe is inserted

bombardment for excitation was demonstrated by Johansson et al. (1970), who reported an interference-free signal in the picogram (10^{-12} g) range. The excellent capability of accelerator beams for X-ray emission analysis is partially due to the relatively low background radiation associated with the excitation. The high particle fluxes obtainable from accelerators also contribute to the sensitivity of the PIXE method. Literature reviews (Folkmann et al., 1974; Gilfrich et al., 1973; Herman et al., 1973; Walter et al., 1974) on approaches to X-ray elemental analysis agree that protons of a few MeV energy provide a preferred combination for high sensitivity analysis under conditions less subject to matrix interference effects. As a result of this premise, a system designed for routine analysis has been described (Johansson et al., 1975) and papers involving the use of PIXE for aerosol analysis have appeared (Hardy et al., 1976; Johansson et al., 1975). The use of radionuclides to excite X-ray fluorescence and to determine lead in airborne particles has also been described (Havranek and Bumbalova, 1981; Havranek et al., 1980).

X-radiation is the basis of the electron microprobe method of analysis. When an intense electron beam is incident on a sample, it produces several forms of radiation, including X-rays, whose wavelengths depend on the elements present in the material and whose intensities depend on the relative quantities of these elements. An electron beam that gives a spot size as small as 0.2 μm is possible. The microprobe is often incorporated in a scanning electron microscope that allows precise location of the beam and comparison of the sample morphology with its elemental composition. Under ideal conditions, the analysis is quantitative, with an accuracy of a few percent. The mass of the analyzed element may range from 10^{-14} to 10^{-16} g (McKinley et al., 1966).

Electron microprobe analysis is not a widely applicable monitoring method. It requires expensive equipment, complex sample preparation procedures, and a highly trained operator. The method is unique, however, in providing compositional information on individual lead particles, thus permitting the study of dynamic chemical changes and perhaps allowing improved source identification.

Advantages of X-ray fluorescence methods include the ability to detect a variety of elements, the ability to analyze with little or no sample preparation, low detection limits (2 ng Pb/m^3) and the availability of automated analytical equipment. Disadvantages are that the X-ray analysis requires liquid nitrogen (e.g., for energy-dispersive models) and highly trained analysts. The detection limit for lead is approximately 9 ng/cm^2 of filter area (Jaklevic and Walter, 1977), which is well below the quantity obtained in normal sampling periods with the dichotomous sampler (Dzubay and Stevens, 1975).

In the bag technique, auto emissions produced during simulated driving cycles are air-diluted and collected in a large plastic bag. The aerosol sample is passed through a filtration or impaction sampler prior to lead analysis (Ter Haar et al., 1972). This technique may result in errors of aerosol size analysis because of condensation of low vapor pressure organic substances onto the lead particles.

To minimize condensation problems, a third technique, a low residence time proportional sampling system, has been used. It is based on proportional sampling of raw exhaust, again diluted with ambient air followed by filtration or impaction (Ganley and Springer, 1974; Sampson and Springer, 1973). Since the sample flow must be a constant proportion of the total exhaust flow, this technique may be limited by the response time of the equipment to operating cycle phases that cause relatively small transients in the exhaust flow rate.

4.2.4 Sampling for Lead in Other Media

Other primary environmental media that may be affected by airborne lead include precipitation, surface water, soil, vegetation, and foodstuffs. The sampling plans and the sampling methodologies used in dealing with these media depend on the purpose of the experiments, the types of measurements to be carried out, and the analytical technique to be used. General approaches are given below in lieu of specific procedures associated with the numerous possible special situations.

4.2.4.1 Precipitation. The investigator should be aware that dry deposition occurs continuously, that lead at the start of a rain event is higher in concentration than at the end, and that rain striking the canopy of a forest may rinse dry deposition particles from the leaf surfaces. Rain collection systems should be designed to collect precipitation on an event basis and to collect sequential samples during the event. They should be tightly sealed from the atmosphere before and after sampling to prevent contamination from dry deposition, falling leaves, and flying insects. Samples should be acidified to pH 1 with nitric acid and refrigerated immediately after sampling. All collection and storage surfaces should be thoroughly cleaned and free of contamination.

Two automated systems have been in use for some time. The Sangamo Precipitation Collector, Type A, collects rain in a single bucket exposed at the beginning of the rain event (Samant and Vaidya, 1982). These authors reported no leaching of lead from the bucket into a solution of 0.3N HNO_3. A second sampler, described by Coscio et al. (1982), also remains covered between rain events; it can collect a sequence of eight samples during the period of rain and may be fitted with a refrigeration unit for sample cooling. No reports of lead analyses were given. Because neither system is widely used, their monitoring effectiveness has not been thoroughly evaluated.

electrochemical methods generally offer sufficient analytical sensitivity for most lead measurement problems. Differential pulse polarography (DPP) relies on the measurement of the faradaic current for lead as the voltage is scanned while compensating for the nonfaradaic (background) current produced (McDonnell, 1981). Anodic stripping voltammetry (ASV) is a two step process in which the lead is preconcentrated onto a mercury electrode by an extended but selected period of reduction. After the reduction step, the potential is scanned either linearly or by differential pulse to oxidize the lead and allow measurement of the oxidation (stripping) current. The preconcentration step allows development of enhanced analytical signals; when used in combination with the differential pulse method lead concentrations at the subnanogram level can be measured (Florence, 1980).

The ASV method has been widely applied to the analysis of atmospheric lead (Harrison et al., 1971; Khandekar et al., 1981; MacLeod and Lee, 1973). Landy (1980) has shown the applicability to the determination of Cd, Cu, Pb, and Zn in Antarctic snow while Nguyen et al. (1979) have analyzed rain water and snow samples. Green et al. (1981) have used the method to determine Cd, Cu, and Pb in sea water. The ASV determination of Cd, Cu, Pb, and Zn in foods has been described by Jones et al., 1977; Mannino, 1982; and Satzger et al., 1982, and the general accuracy of the method summarized by Holak (1980). Current practice with commercially available equipment allows lead analysis at subnanogram concentrations with precision at the 5 to 10 percent on a routine basis (Skogerboe et al., 1977b). New developments center around the use of microcomputers in controlling the stripping voltage (Kryger, 1981) and conformational modifications of the electrode (Brihaye and Duyckaerts, 1982).

4.3.7 Methods for Compound Analysis

The majority of analytical methods are restricted to measurement of total lead and cannot directly identify the various compounds of lead. The electron microprobe and other X-ray fluorescence methods provide approximate data on compounds on the basis of the ratios of elements present (Ter Haar and Bayard, 1971). Gas chromatography (GC) using the electron capture detector has been demonstrated to be useful for organolead compounds (Shapiro and Frey, 1968). The use of atomic absorption as the GC detector for organolead compounds has been described by DeJonghe et al. (1981), while a plasma emission detector has been used by Estes et al. (1981). In addition, Messman and Rains (1981) have used liquid chromatography with an atomic absorption detector to measure organolead compounds. Mass spectrometry may also be used with gas chromatography (Mykytiuk et al., 1980).

Powder X-ray diffraction techniques have been applied to the identification of lead compounds in soils by Olson and Skogerboe (1975) and by Linton et al. (1980). X-ray diffraction techniques were used (Harrison and Perry, 1977; Foster and Lott, 1980; Jacklevic et al., 1981) to identify lead compounds collected on air filters.

4.2.4.4 Vegetation. Because most soil lead is in forms unavailable to plants, and because lead is not easily transported by plants, roots typically contain very little lead and shoots even less (Zimdahl, 1976; Zimdahl and Koeppe, 1977). Before analysis, a decision must be made as to whether or not the plant material should be washed to remove surface contamination from dry deposition and soil particles. If the plants are sampled for total lead content (e.g., if they serve as animal food sources), they cannot be washed. If the effect of lead on internal plant processes is being studied, the plant samples should be washed. In either case, the decision must be made at the time of sampling, as washing cannot be effective after the plant materials have dried. Fresh plant samples cannot be stored for any length of time in a tightly closed container before washing because molds and enzymatic action may affect the distribution of lead on and in the plant tissues. Freshly picked leaves stored in sealed polyethylene bags at room temperature generally begin to decompose in a few days. Storage time may be increased to approximately 2 weeks by refrigeration.

After collection, plant samples should be dried as rapidly as possible to minimize chemical and biological changes. Samples that are to be stored for extended periods of time should be oven dried to arrest enzymatic reactions and render the plant tissue amenable to grinding. Storage in sealed containers is required after grinding. For analysis of surface lead, fresh, intact plant parts are agitated in dilute nitric acid or EDTA solutions for a few seconds.

4.2.4.5 Foodstuffs. From 1972 to 1978, lead analysis was included in the Food and Drug Administration Market Basket Survey, which involves nationwide sampling of foods representing the average diet of an 18-year-old male, i.e., the individual who on a statistical basis eats the greatest quantity of food (Kolbye et al., 1974). Various food items from the several food classes are purchased in local markets and made up into meal composites in the proportion that each food item is ingested; they are then cooked or otherwise prepared as they would be consumed. Foods are grouped into 12 food classes, then composited and analyzed chemically. Other sampling programs may be required for different investigative purposes. For those foods where lead may be deposited on the edible portion, the question of whether or not to use typical kitchen washing procedures before analysis should be considered in the context of the experimental purpose.

4.2.5 Filter Selection and Sample Preparation

In sampling for airborne lead, air is drawn through filter materials such as glass fiber, cellulose acetate, or porous plastic (Skogerboe et al., 1977b, Stern, 1968). These materials often include contaminant lead that can interfere with the subsequent analysis (Gandrud and Lazrus, 1972; Kometani et al. 1972; Luke et al., 1972; Seeley and Skogerboe, 1974). If the

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With respect to measuring lead without sampling or laboratory contamination, several investigators have shown that the magnitude of the problem is quite large (Patterson and Settle, 1976; Patterson et al., 1976; Pierce et al., 1976; Patterson, 1982; Skogerboe, 1982). It appears that the problem may be caused by failure to control the blank or by failure to standardize instrument operation (Patterson, 1982; Skogerboe, 1982). The laboratory atmosphere, collecting containers, and the labware used may be primary contributors to the lead blank problem (Murphy, 1976; Patterson, 1982; Skogerboe, 1982). Failure to recognize these and other sources such as reagents and hand contact is very likely to result in the generation of artificially high analytical results. Samples with less than 100 µg Pb should be analyzed in a clean laboratory especially designed for the elimination of lead contamination. Moody (1982) has described the construction and application of such a laboratory at the National Bureau of Standards.

For many analytical techniques, a preconcentration step is recommended. Leyden and Wegschelder (1981) have described several procedures and the associated problems with controlling the analytical blank. There are two steps to preconcentration. The first is the removal of organic matter by dry ashing or wet digestion. The second is the separation of lead from interfering metallic elements by coprecipitation or passing through a resin column. New separation techniques are continuously being evaluated, many of which have application to specific analytical problems. Yang and Yeh (1982) have described a polyacrylamide-hydrous-zirconia (PHZ) composite ion exchanger suitable for high phosphate solutions. Corsini, et al. (1982) evaluated a macroreticular acrylic ester resin capable of removing free and inorganically bound metal ions directly from aqueous solution without prior chelation.

4.3.1 Atomic Absorption Spectroscopy (AAS)

Atomic absorption spectroscopy (AAS) is a widely accepted method for the measurement of lead in environmental sampling (Skogerboe et al., 1977b). A variety of lead studies using AAS have been reported (Kometani et al., 1972; Zoller et al., 1974; Huntzicker et al., 1975; Scott et al., 1976b; Lester et al., 1977; Hirao et al., 1979; Compton and Thomas, 1980; Bertenshaw and Gelsthorpe, 1981).

The lead atoms in the sample must be vaporized either in a precisely controlled flame or in a furnace. Furnace systems in AAS offer high sensitivity as well as the ability to analyze small samples (Lester et al., 1977; Rouseff and Ting, 1980; Stein et al., 1980; Bertenshaw et al., 1981). These enhanced capabilities are offset in part by greater difficulty in analytical calibration and by loss of analytical precision.

4.4 CONCLUSIONS

To monitor lead particles in air, collection with the hi-vol and dichotomous samplers and analysis by atomic absorption spectrometry and X-ray fluorescence methods have emerged as the most widely used methods. Sampling with the hi-vol has inherent biases in sampling large particles and does not provide for fractionation of the particles according to size, nor does it allow determination of the gaseous (organic) concentrations. Sampling with a dichotomous sampler provides size information but does not allow for gaseous lead measurements. The size distribution of lead aerosol particles is important in considering inhalable particulate matter. To determine gaseous lead, it is necessary to back up the filter with chemical scrubbers such as a crystalline iodine trap.

X-ray fluorescence and optical emission spectroscopy are applicable to multi-element analysis. Other analytical techniques find application for specific purposes. The paucity of data on the types of lead compounds at subnanogram levels in the ambient air is currently being addressed through development of improved XRF analyzer procedures.

Scott et al. (1976a) analyzed composited particulate samples obtained with hi-vols for about 24 elements, including lead, using a direct reading emission spectrometer. Over 1000 samples collected by the NASN in 1970 were analyzed. Careful consideration of accuracy and precision led to the conclusion that optical emission spectroscopy is a rapid and practical technique for particle analysis.

More recent activities have focused attention on the inductively coupled plasma (ICP) system as a valuable means of excitation and analysis (Garbarino and Taylor, 1979; Winge et al., 1977). The ICP system offers a higher degree of sensitivity with less analytical interference than is typical of many of the other emission spectroscopic systems. Optical emission methods are inefficient when used for analysis of a single element, since the equipment is expensive and a high level of operator training is required. This problem is largely offset when analysis for several elements is required as is often the case for atmospheric aerosols.

4.3.3 X-Ray Fluorescence (XRF)

X-ray emissions that characterize the elemental content of a sample also occur when atoms are irradiated at sufficient energy to excite an inner-shell electron (Hammerle and Pierson, 1975; Jaklevic et al., 1973; Skogerboe et al., 1977b; Stevens et al., 1978). This fluorescence allows simultaneous identification of a range of elements including lead.

X-ray fluorescence may require a high-energy irradiation source. But with the X-ray tubes coupled with fluorescers (Jaklevic et al., 1973; Dzubay and Stevens, 1975; Paciga and Jervis, 1976) very little energy is transmitted to the sample, thus sample degradation is kept to a minimum (Shaw et al., 1980). Electron beams (McKinley et al., 1966), and radioactive isotope sources (Kneip and Laurer 1972) have been used extensively (Birks et al., 1971; Birks, 1972) as energy sources for XRF analysis. To reduce background interference, secondary fluorescers have been employed (Birks et al., 1971; Dzubay and Stevens, 1975). The fluorescent X-ray emission from the sample may be analyzed with a crystal monochromator and detected with scintillation or proportional counters (Skogerboe et al., 1977b) or with low-temperature semiconductor detectors that discriminate the energy of the fluorescence. The latter technique requires a very low level of excitation (Dzubay and Stevens, 1975; Toussaint and Boniforti, 1979).

X-ray emission induced by charged-particle excitation (proton-induced X-ray emission or PIXE) offers an attractive alterative to the more common techniques (Barfoot et al., 1979; Hardy et al., 1976; Johansson et al., 1970). Recognition of the potential of heavy-particle

4.3.4 Mass Spectrometry

Isotope dilution mass spectrometry (IDMS) is an absolute measurement technique. It serves as the standard to which other analytical techniques are compared. No other techniques serve more reliably as a comparative reference. Its use for analyses at subnanogram concentrations of lead and in a variety of sample types has been reported (Chow et al., 1969, 1974; Facchetti and Geiss, 1982; Hirao and Patterson, 1974; Murozumi et al., 1969; Patterson et al., 1976; Rabinowitz et al., 1973).

The isotopic composition of lead peculiar to various ore bodies and crustal sources may also be used as a means of tracing the origin of anthropogenic lead. Other examples of IDMS application are found in several reports cited above, and in Rabinowitz and Wetherill (1972), Stacey and Kramers (1975), and Machlan et al. (1976).

4.3.5 Colorimetric Analysis

Colorimetric or spectrophotometric analysis for lead using dithizone (diphenylthiocarbazone) as the reagent has been used for many years (Anonymous, 1963; Horowitz et al., 1970; Sandell, 1944). It was the primary method recommended by a National Academy of Sciences (1972) report on lead, and the basis for the tentative method of testing for lead in the atmosphere by the American Society for Testing and Materials (1975b). Prior to the development of the IDMS method, colorimetric analysis served as the reference by which other methods were tested.

The procedures for the colorimetric analysis require a skilled analyst if reliable results are to be obtained. The ASTM conducted a collaborative test of the method (Foster et al., 1975) and concluded that the procedure gave satisfactory precision in the determination of particulate lead in the atmosphere. In addition, the required apparatus is simple and relatively inexpensive, the absorption is linearly related to the lead concentration, large samples can be used, and interferences can be removed (Skogerboe et al., 1977b). Realization of these advantages depends on meticulous attention to the procedures and reagents.

4.3.6 Electrochemical Methods: Anodic Stripping Voltammetry (ASV), Differential Pulse Polarography (DPP)

Analytical methods based on electrochemical phenomena are found in a variety of forms (Sawyer and Roberts, 1974; Willard et al., 1974). They are characterized by a high degree of sensitivity, selectivity, and accuracy derived from the relationship between current, charge, potential, and time for electrolytic reactions in solutions. The electrochemistry of lead is based primarily on Pb(II), which behaves reversibly in ionic solutions having a reduction potential near -0.4 volt versus the standard calomel electrode (Skogerboe et al., 1977b). Two

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ABSTRACT

The document evaluates and assesses scientific information on the health and welfare effects associated with exposure to various concentrations of lead in ambient air. The literature through 1983 has been reviewed thoroughly for information relevant to air quality criteria, although the document is not intended as a complete and detailed review of all literature pertaining to lead. An attempt has been made to identify the major discrepancies in our current knowledge and understanding of the effects of these pollutants.

Although this document is principally concerned with the health and welfare effects of lead, other scientific data are presented and evaluated in order to provide a better understanding of this pollutant in the environment. To this end, the document includes chapters that discuss the chemistry and physics of the pollutant; analytical techniques; sources, and types of emissions; environmental concentrations and exposure levels; atmospheric chemistry and dispersion modeling; effects on vegetation; and respiratory, physiological, toxicological, clinical, and epidemiological aspects of human exposure.

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AAS	Atomic absorption spectrometry
Ach	Acetylcholine
ACTH	Adrenocoticotrophic hormone
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADP/O ratio	Adenosine diphosphate/oxygen ratio
AIDS	Acquired immune deficiency syndrome
AIHA	American Industrial Hygiene Association
AII	Angiotensin II
ALA	Aminolevulinic acid
ALA-D	Aminolevulinic acid dehydrase
ALA-S	Aminolevulinic acid synthetase
ALA-U	Aminolevulinic acid in urine
APDC	Ammonium pyrrolidine-dithiocarbamate
APHA	American Public Health Association
ASTM	Amercian Society for Testing and Materials
ASV	Anodic stripping voltammetry
ATP	Adenosine triphosphate
B-cells	Bone marrow-derived lymphocytes
Ba	Barium
BAL	British anti-Lewisite (AKA dimercaprol)
BAP	benzo(a)pyrene
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
BW	Body weight
C.V.	Coefficient of variation
CaBP	Calcium binding protein
CaEDTA	Calcium ethylenediaminetetraacetate
CBD	Central business district
Cd	Cadmium
CDC	Centers for Disease Control
CEC	Cation exchange capacity
CEH	Center for Environmental Health
CFR	reference method
CMP	Cytidine monophosphate
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CP-U	Urinary coproporphyrin
C_{Cpah}	plasma clearance of p-aminohippuric acid
Cu	Copper
D.F.	Degrees of freedom
DA	Dopamine
DCMU	[3-(3,4-dichlorophenyl)-1,1-dimethylurea
DDP	Differential pulse polarography
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
EEC	European Economic Community
EEG	Electroencephalogram
EMC	Encephalomyocarditis
EP	Erythrocyte protoporphyrin
EPA	U.S. Environmental Protection Agency

LIST OF ABBREVIATIONS (continued).

FA	Fulvic acid
FDA	Food and Drug Administration
Fe	Iron
FEP	Free erythrocyte protoporphyrin
FY	Fiscal year
G.M.	Grand mean
G-6-PD	Glucose-6-phosphate dehydrogenase
GABA	Gamma-aminobutyric acid
GALT	Gut-associated lymphoid tissue
GC	Gas chromatography
GFR	Glomerular filtration rate
HA	Humic acid
Hg	Mercury
hi-vol	High-volume air sampler
HPLC	High-performance liquid chromatography
i.m.	Intramuscular (method of injection)
i.p.	Intraperitoneally (method of injection)
i.v.	Intravenously (method of injection)
IAA	Indol-3-ylacetic acid
IARC	International Agency for Research on Cancer
ICD	International classification of diseases
ICP	Inductively coupled plasma
IDMS	Isotope dilution mass spectrometry
IF	Interferon
ILE	Isotopic Lead Experiment (Italy)
IRPC	International Radiological Protection Commission
K	Potassium
LAI	Leaf area index
LDH-X	Lactate dehydrogenase isoenzyme x
LC_{50}	Lethyl concentration (50 percent)
LD_{50}	Lethal dose (50 percent)
LH^{50}	Luteinizing hormone
LIPO	Laboratory Improvement Program Office
ln	National logarithm
LPS	Lipopolysaccharide
LRT	Long range transport
mRNA	Messenger ribonucleic acid
ME	Mercaptoethanol
MEPP	Miniature end-plate potential
MES	Maximal electroshock seizure
MeV	Mega-electron volts
MLC	Mixed lymphocyte culture
MMD	Mass median diameter
MMED	Mass median equivalent diameter
Mn	Manganese
MND	Motor neuron disease
MSV	Moloney sarcoma virus
MTD	Maximum tolerated dose
n	Number of subjects
N/A	Not Available

LIST OF ABBREVIATIONS (continued)

NA	Not Applicable
NAAQS	National ambient air quality standards
NADB	National Aerometric Data Bank
NAMS	National Air Monitoring Station
NAS	National Academy of Sciences
NASN	National Air Surveillance Network
NBS	National Bureau of Standards
NE	Norepinephrine
NFAN	National Filter Analysis Network
NFR-82	Nutrition Foundation Report of 1982
NHANES II	National Health Assessment and Nutritional Evaluation Survey II
Ni	Nickel
OSHA	Occupational Safety and Health Administration
P	Potassium
p	Significance symbol
PAH	Para-aminohippuric acid
Pb	Lead
PBA	Air lead
$Pb(Ac)_2$	Lead acetate
PbB	concentration of lead in blood
PbBrCl	Lead (II) bromochloride
PBG	Porphobilinogen
PFC	Plaque-forming cells
pH	Measure of acidity
PHA	Phytohemagglutinin
PHZ	Polyacrylamide-hydrous-zirconia
PIXE	Proton-induced X-ray emissions
PMN	Polymorphonuclear leukocytes
PND	Post-natal day
PNS	Peripheral nervous system
ppm	Parts per million
PRA	Plasma renin activity
PRS	Plasma renin substrate
PWM	Pokeweed mitogen
Py-5-N	Pyrimide-5'-nucleotidase
RBC	Red blood cell; erythrocyte
RBF	Renal blood flow
RCR	Respiratory control ratios/rates
redox	Oxidation-reduction potential
RES	Reticuloendothelial system
RLV	Rauscher leukemia virus
RNA	Ribonucleic acid
S-HT	Serotonin
SA-7	Simian adenovirus
scm	Standard cubic meter
S.D.	Standard deviation
SDS	Sodium dodecyl sulfate
S.E.M.	Standard error of the mean
SES	Socioeconomic status
SGOT	Serum glutamic oxaloacetic transaminase

LIST OF ABBREVIATIONS (continued).

sIg	Surface immunoglobulin
SLAMS	State and local air monitoring stations
SMR	Standardized mortality ratio
Sr	Strontium
SRBC	Sheep red blood cells
SRMs	Standard reference materials
STEL	Short-term exposure limit
SW voltage	Slow-wave voltage
T-cells	Thymus-derived lymphocytes
t-tests	Tests of significance
TBL	Tri-n-butyl lead
TEA	Tetraethyl-ammonium
TEL	Tetraethyllead
TIBC	Total iron binding capacity
TML	Tetramethyllead
TMLC	Tetramethyllead chloride
TSH	Thyroid-stimulating hormone
TSP	Total suspended particulate
U.K.	United Kingdom
UMP	Uridine monophosphate
USPHS	U.S. Public Health Service
VA	Veterans Administration
V_d	Deposition velocity
VER	Visual evoked response
WHO	World Health Organization
XRF	X-Ray fluorescence
X^2	Chi squared
Zn	Zinc
ZPP	Erythrocyte zinc protoporphyrin

MEASUREMENT ABBREVIATIONS

dl	deciliter
ft	feet
g	gram
g/gal	gram/gallon
g/ha·mo	gram/hectare·month
km/hr	kilometer/hour
l/min	liter/minute
mg/km	milligram/kilometer
$\mu g/m^3$	microgram/cubic meter
mm	millimeter
µmol	micrometer
ng/cm^2	nanograms/square centimeter
nm	namometer
nM	nanomole
sec	second

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2. INTRODUCTION

According to Section 108 of the Clean Air Act of 1970, as amended in June 1974, a criteria document for a specific pollutant or class of pollutants shall

> . . . accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities.

Air quality criteria are of necessity based on presently available scientific data, which in turn reflect the sophistication of the technology used in obtaining those data as well as the magnitude of the experimental efforts expended. Thus air quality criteria for atmospheric pollutants are a scientific expression of current knowledge and uncertainties. Specifically, air quality criteria are expressions of the scientific knowledge of the relationships between various concentrations--averaged over a suitable time period--of pollutants in the same atmosphere and their adverse effects upon public health and the environment. Criteria are issued to help make decisions about the need for control of a pollutant and about the development of air quality standards governing the pollutant. Air quality criteria are descriptive; that is, they describe the effects that have been observed to occur as a result of external exposure at specific levels of a pollutant. In contrast, air quality standards are prescriptive; that is, they prescribe what a political jurisdiction has determined to be the maximum permissible exposure for a given time in a specified geographic area.

In the case of criteria for pollutants that appear in the atmosphere only in the gas phase (and thus remain airborne), the sources, levels, and effects of exposure must be considered only as they affect the human population through inhalation of or external contact with that pollutant. Lead, however, is found in the atmosphere primarily as inorganic particulate, with only a small fraction normally occurring as vapor-phase organic lead. Consequently, inhalation and contact are but two of the routes by which human populations may be exposed to lead. Some particulate lead may remain suspended in the air and enter the human body only by inhalation, but other lead-containing particles will be deposited on vegetation, surface waters, dust, soil, pavements, interior and exterior surfaces of housing--in fact, on any surface in contact with the air. Thus criteria for lead must be developed that will take into account all principal routes of exposure of the human population.

This criteria document is a revision of the previous Air Quality Criteria Document for Lead (EPA-600/8-77-017) published in December, 1977. This revision is mandated by the Clean Air Act (Sect. 108 and 109), as amended U.S.C. §§7408 and 7409. The criteria document sets forth what is known about the effects of lead contamination in the environment on human health and welfare. This requires that the relationship between levels of exposure to lead,

via all routes and averaged over a suitable time period, and the biological responses to those levels be carefully assessed. Assessment of exposure must take into consideration the temporal and spatial distribution of lead and its various forms in the environment.

This document focuses primarily on lead as found in its various forms in the ambient atmosphere; in order to assess its effects on human health, however, the distribution and biological availability of lead in other environmental media have been considered. The rationale for structuring the document was based primarily on the two major questions of exposure and response. The first portion of the document is devoted to lead in the environment--its physical and chemical properties; the monitoring of lead in various media; sources, emissions, and concentrations of lead; and the transport and transformation of lead within environmental media. The later chapters are devoted to discussion of biological responses and effects on ecosystems and human health.

In order to facilitate printing, distribution, and review of the present draft materials, this First External Review Draft of the revised EPA Air Quality Criteria Document for Lead is being released in the form of four volumes. The first volume (Volume I) contains the executive summary and conclusions chapter (Chapter 1) for the entire document. Volume II (the present volume) contains Chapters 2-8, which include: the introduction for the document (Chapter 2); discussions of the above listed topics concerning lead in the environment (Chapters 3-7); and evaluation of lead effects on ecosystems (Chapter 8). The remaining two volumes contain Chapters 9-13, which deal with the extensive available literature relevant to assessment of health effects associated with lead exposure.

An effort has been made to limit the document to a highly critical assessment of the scientific data base. The scientific literature has been reviewed through June 1983. The references cited do not constitute an exhaustive bibliography of all available lead-related literature but they are thought to be sufficient to reflect the current state of knowledge on those issues most relevant to the review of the air quality standard for lead.

The status of control technology for lead is not discussed in this document. For information on the subject, the reader is referred to appropriate control technology documentation published by the Office of Air Quality Planning and Standards (OAQPS), EPA. The subject of adequate margin of safety stipulated in Section 108 of the Clean Air Act also is not explicity addressed here; this topic will be considered in depth by EPA's Office of Air Quality Planning and Standards in documentation prepared as a part of the process of revising the National Ambient Air Quality Standard for Lead.

3. CHEMICAL AND PHYSICAL PROPERTIES

3.1 INTRODUCTION

Lead is a gray-white metal of bright luster that, because of its easy isolation and low melting point (327.5°C), was among the first of the metals to be placed in the service of man. Lead was used as early as 2000 B.C. by the Phoenicians, who traveled as far as Spain and England to mine it, and it was used extensively by the Egyptians; the British Museum contains a lead figure found in an Egyptian temple which possibly dates from 3000 B.C. The most abundant ore is galena, in which lead is present as the sulfide (PbS), and from which metallic lead is readily smelted. The metal is soft, malleable, and ductile, a poor electrical conductor, and highly impervious to corrosion. This unique combination of physical properties has led to its use in piping and roofing, and in containers for corrosive liquids. By the time of the Roman Empire, it was already in wide use in aqueducts and public water systems, as well as in cooking and storage utensils. Its alloys are used as solder, type metal, and various antifriction materials. The metal and the dioxide are used in storage batteries, and much metal is used in cable covering, plumbing and ammunition. Because of its high nuclear cross section, lead is extensively used as a radiation shield around X-ray equipment and nuclear reactors.

3.2 ELEMENTAL LEAD

In comparison with the most abundant metals in the earth's crust (aluminum and iron), lead is a rare metal; even copper and zinc are more abundant by factors of five and eight, respectively. Lead is, however, more abundant than the other toxic heavy metals; its abundance in the earth's crust has been estimated (Moeller, 1952) to be as high as 1.6×10^{-3} percent, although some other authors (Heslop and Jones, 1976) suggest a lower value of 2×10^{-4} percent. Either of these estimates suggests that the abundance of lead is more than 100 times that of cadmium or mercury, two other significant systemic metallic poisons. More important, since lead occurs in highly concentrated ores from which it is readily separated, the availability of lead is far greater than its natural abundance would suggest. The great environmental significance of lead is the result both of its utility and of its availability. Lead ranks fifth among metals in tonnage consumed, after iron, copper, aluminum and zinc; it is, therefore, produced in far larger quantities than any other toxic heavy metal (Dyrssen, 1972). The properties of elemental lead are summarized in Table 3-1.

TABLE 3-1. PROPERTIES OF ELEMENTAL LEAD

Property	Description
Atomic weight	207.19
Atomic number	82
Oxidation states	+2, +4
Density	11.35 g/cm^3 at 20 °C
Melting point	327.5 °C
Boiling point	1740 °C
Covalent radius (tetradehral)	1.44 Å
Ionic radii	1.21 Å (+2), 0.78 Å (+4)
Resistivity	21.9×10^{-6} ohm/cm

Natural lead is a mixture of four stable isotopes: ^{204}Pb (~1.5 percent), ^{206}Pb (23.6 percent), ^{207}Pb (22.6 percent), and ^{208}Pb (52.3 percent). There is no radioactive progenitor for ^{204}Pb, but ^{206}Pb, ^{207}Pb, and ^{208}Pb are produced by the radioactive decay of ^{238}U, ^{235}U, and ^{232}Th, respectively. There are four radioactive isotopes of lead that occur as members of these decay series. Of these, only ^{210}Pb is long lived, with a half-life of 22 years. The others are ^{211}Pb (half-life 36.1 min), ^{212}Pb (10.64 hr), and ^{214}Pb (26.8 min). The stable isotopic compositions of naturally occurring lead ores are not identical, but show variations reflecting geological evolution (Russell and Farquhar, 1960). Thus, the observed isotopic ratios depend upon the U/Pb and Th/Pb ratios of the source from which the ore is derived and the age of the ore deposit. The $^{206}Pb/^{204}Pb$ isotopic ratio, for example, varies from approximately 16.5 to 21 depending on the source (Doe, 1970). The isotopic ratios in average crustal rock reflect the continuing decay of uranium and thorium. The differences between crustal rock and ore bodies, and between major ore bodies in various parts of the world, often permit the identification of the source of lead in the environment.

3.3 GENERAL CHEMISTRY OF LEAD

Lead is the heaviest element in Group IVB of the periodic table; this is the group that also contains carbon, silicon, germanium, and tin. Unlike the chemistry of carbon, however, the inorganic chemistry of lead is dominated by the divalent (+2) oxidation state rather than

the tetravalent (+4) oxidation state. This important chemical feature is a direct result of the fact that the strengths of single bonds between the Group IV atoms and other atoms generally decrease as the atomic number of the Group IV atom increases (Cotton and Wilkinson, 1980). Thus, the average energy of a C-H bond is 100 kcal/mole, and it is this factor that stabilizes CH_4 relative to CH_2; for lead, the Pb-H energy is only approximately 50 kcal/mole (Shaw and Allred, 1970), and this is presumably too small to compensate for the Pb(II) → Pb(IV) promotional energy. It is this same feature that explains the marked difference in the tendencies to catenation shown by these elements. Though C-C bonds are present in literally millions of compounds, for lead catenation occurs only in organolead compounds. Lead does, however, form compounds like Na_4Pb_9 which contain distinct polyatomic lead clusters (Britton, 1964), and Pb-Pb bonds are found in the cationic cluster $[Pb_6O(OH)_6]^{+4}$ (Olin and Soderquist, 1972).

A listing of the solubilities and physical properties of the more common compounds of lead is given in Appendix 3A. As can be discerned from those data, most inorganic lead salts are sparingly soluble (e.g., PbF_2, $PbCl_2$) or virtually insoluble ($PbSO_4$, $PbCrO_4$) in water; the notable exceptions are lead nitrate, $Pb(NO_3)_2$, and lead acetate, $Pb(OCOCH_3)_2$. Inorganic lead (II) salts are, for the most part, relatively high-melting-point solids with correspondingly low vapor pressures at room temperatures. The vapor pressures of the most commonly encountered lead salts are also tabulated in Appendix 3A. The transformation of lead salts in the atmosphere is discussed in Chapter 6.

3.4 ORGANOMETALLIC CHEMISTRY OF LEAD

The properties of organolead compounds (i.e., compounds containing bonds between lead and carbon) are entirely different from those of the inorganic compounds of lead; although a few organolead(II) compounds, such as dicyclopentadienyllead, $Pb(C_5H_5)_2$, are known, the organic chemistry of lead is dominated by the tetravalent (+4) oxidation state. An important property of most organolead compounds is that they undergo photolysis when exposed to light (Rufman and Rotenberg, 1980).

Because of their use as antiknock agents in gasoline and other fuels, the most important organolead compounds have been the tetraalkyl compounds tetraethyllead (TEL) and tetramethyllead (TML). As would be expected for such nonpolar compounds, TEL and TML are insoluble in water but soluble in hydrocarbon solvents (e.g., gasoline). These two compounds are manufactured by the reaction of the alkyl chloride with lead-sodium alloy (Shapiro and Frey, 1968):

$$4NaPb + 4C_2H_5Cl \rightarrow (C_2H_5)_4Pb + 3Pb + 4NaCl \qquad (3\text{-}1)$$

The methyl compound, TML, is also manufactured by a Grignard process involving the electrolysis of lead pellets in methylmagnesium chloride (Shapiro and Frey, 1968):

$$2CH_3MgCl + 2CH_3Cl + Pb \rightarrow (CH_3)_4Pb + 2MgCl_2 \quad (3\text{-}2)$$

A common type of commercial antiknock mixture contains a chemically redistributed mixture of alkyllead compounds. In the presence of Lewis acid catalysts, a mixture of TEL and TML undergoes a redistribution reaction to produce an equilibrium mixture of the five possible tetraalkyllead compounds. For example, an equimolar mixture of TEL and TML produces a product with a composition as shown below:

Component	Mol percent
$(CH_3)_4Pb$	4.6
$(CH_3)_3Pb(C_2H_5)$	24.8
$(CH_3)_2Pb(C_2H_5)_2$	41.2
$(CH_3)Pb(C_2H_5)_3$	24.8
$(C_2H_5)_4Pb$	4.6

These lead compounds are removed from internal combustion engines by a process called lead scavenging, in which they react in the combustion chamber with halogenated hydrocarbon additives (notably ethylene dibromide and ethylene dichloride) to form lead halides, usually bromochlorolead(II). Mobile source emissions are discussed in detail in Section 5.3.3.2.

Several hundred other organolead compounds have been synthesized, and the properties of many of them are reported by Shapiro and Frey (1968). The continuing importance of organolead chemistry is demonstrated by a variety of recent publications investigating the syntheses (Hager and Huber, 1980, Wharf et al., 1980) and structures (Barkigia, et al., 1980) of organolead complexes, and by recent patents for lead catalysts (Nishikido, et al., 1980).

3.5 FORMATION OF CHELATES AND OTHER COMPLEXES

The bonding in organometallic derivatives of lead is principally covalent rather than ionic because of the small difference in the electronegativities of lead (1.8) and carbon (2.6). As is the case in virtually all metal complexes, however, the bonding is of the donor-acceptor type, in which both electrons in the bonding orbital originate from the carbon atom.

The donor atoms in a metal complex could be almost any basic atom or molecule; the only requirement is that a donor, usually called a ligand, must have a pair of electrons available

for bond formation. In general, the metal atom occupies a central position in the complex, as exemplified by the lead atom in tetramethyllead (Figure 3-1a) which is tetrahedrally surrounded by four methyl groups. In these simple organolead compounds, the lead is usually present as Pb(IV), and the complexes are relatively inert. These simple ligands, which bind to metal at only a single site, are called monodentate ligands. Some ligands, however, can bind to the metal atom by more than one donor atom, so as to form a heterocyclic ring structure. Rings of this general type are called chelate rings, and the donor molecules which form them are called polydentate ligands or chelating agents. In the chemistry of lead, chelation normally involves Pb(II), leading to kinetically quite labile (although thermodynamically stable) octahedral complexes. A wide variety of biologically significant chelates with ligands, such as amino acids, peptides, nucleotides and similar macromolecules, are known. The simplest structure of this type occurs with the amino acid glycine, as represented in Figure 3-1b for a 1:2 (metal:ligand) complex. The importance of chelating agents in the present context is their widespread use in the treatment of lead and other metal poisoning.

Metals are often classified according to some combination of their electronegativity, ionic radius and formal charge (Ahrland, 1966, 1968, 1973; Basolo and Pearson, 1967; Nieboer and Richardson, 1980; Pearson, 1963, 1968). These parameters are used to construct empirical classification schemes of relative hardness or softness. In these schemes, "hard" metals form strong bonds with "hard" anions and likewise "soft" metals with "soft" anions. Some metals are borderline, having both soft and hard character. Pb(II), although borderline, demonstrates primarily soft character (Figure 3-2). The terms Class A may also be used to refer to hard metals, and Class B to soft metals. Since Pb(II) is a relatively soft (or class B) metal ion, it forms strong bonds to soft donor atoms like the sulfur atoms in the cysteine residues of proteins and enzymes; it also coordinates strongly with the imidazole groups of histidine residues and with the carboxyl groups of glutamic and aspartic acid residues. In living systems, therefore, lead atoms bind to these peptide residues in proteins, thereby preventing the proteins from carrying out their functions by changing the tertiary structure of the protein or by blocking the substrate's approach to the active site of the protein. As has been demonstrated in several studies (Jones and Vaughn, 1978; Williams and Turner, 1981; Williams et al., 1982), there is an inverse correlation between the LD_{50} values of metal complexes and the chemical softness parameter (σp) (Pearson and Mawby, 1967). Thus, for both mice and Drosophila, soft metal ions like lead(II) have been found to be more toxic than hard metal ions (Williams et al., 1982). This classification of metal ions according to their toxicity has been discussed in detail by Nieboer and Richardson (1980). Lead(II) has a higher softness parameter than either cadmium(II) or mercury(II), so lead(II) compounds would not be expected to be as toxic as their cadmium or mercury analogues.

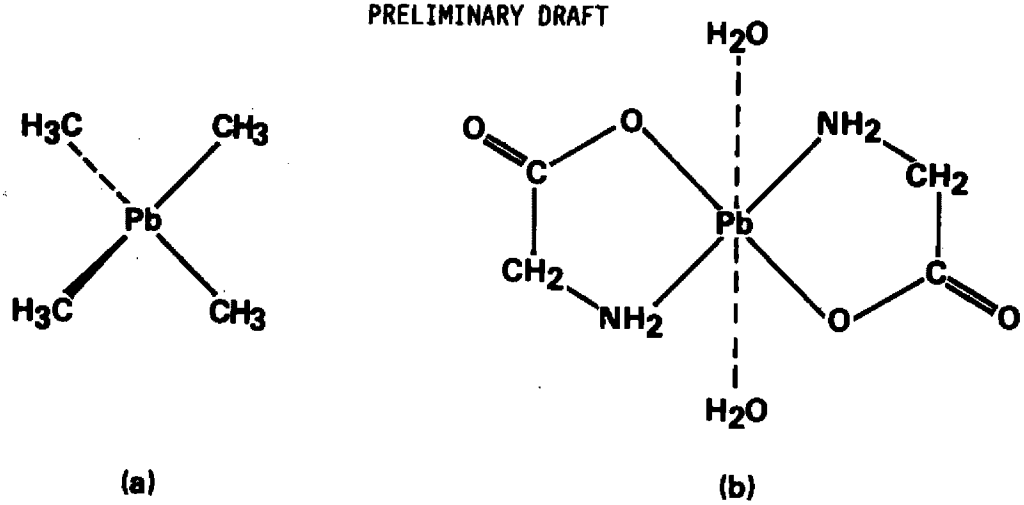

Figure 3-1. Metal complexes of lead.

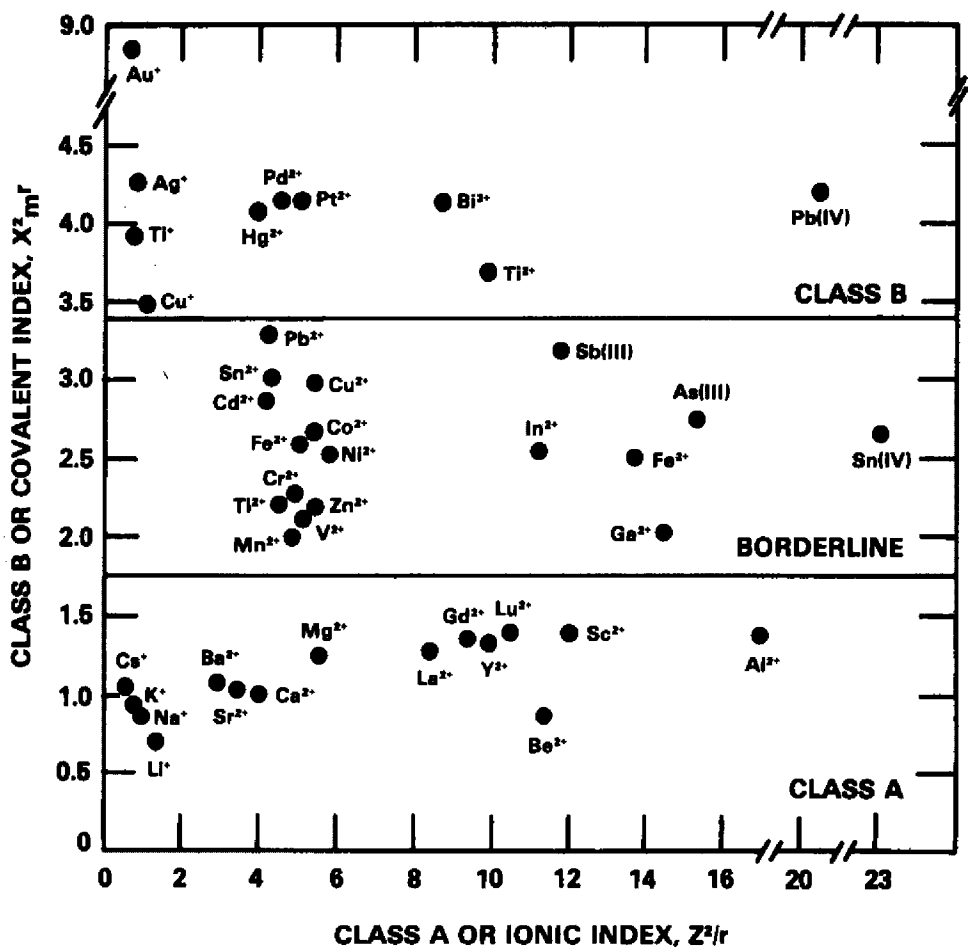

Figure 3-2. Softness parameters of metals.

Source: Nieboer and Richardson (1980).

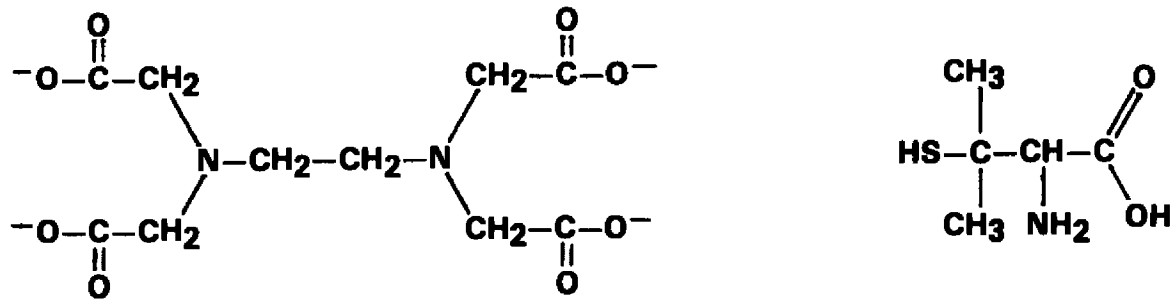

Figure 3-3. Structure of chelating agents.

The role of the chelating agents is to compete with the peptides for the metal by forming stable chelate complexes that can be transported from the protein and eventually be exreted by the body. For simple thermodynamic reasons (see Appendix 3A), chelate complexes are much more stable than monodentate metal complexes, and it is this enhanced stability that is the basis for their ability to compete favorably with proteins and other ligands for the metal ions. The chelating agents most commonly used for the treatment of lead poisoning are ethylenediaminetetraacetate ions (EDTA), D-penicillamine (Figure 3-3) and their derivatives. EDTA is known to act as a hexadentate ligand toward metals (Lis, 1978; McCandlish et al., 1978). X-ray diffraction studies have demonstrated that D-penicillamine is a tridentate ligand binding through its sulfur, nitrogen and oxygen atoms to cobalt (de Meester and Hodgson, 1977a; Helis; et al., 1977), chromium (de Meester and Hodgson, 1977b), cadmium (Freeman et al., 1976), and lead itself (Freeman et al., 1974), but both penicillamine and other cysteine derivatives may act as bidentate ligands (Carty and Taylor, 1977; de Meester and Hodgson, 1977c). Moreover, penicillamine binds to mercury only through its sulfur atoms (Wong et al., 1973; Carty and Taylor, 1976).

It should be noted that both the stoichiometry and structures of metal chelates depend upon pH, and that structures different from those manifest in solution may occur in crystals. It will suffice to state, however, that several ligands can be found that are capable of sufficiently strong chelation with lead present in the body under physiological conditions to permit their use in the effective treatment of lead poisoning.

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APPENDIX 3A

PHYSICAL/CHEMICAL DATA FOR LEAD COMPOUNDS

3A.1 DATA TABLES

Table 3A-1. PHYSICAL PROPERTIES OF INORGANIC LEAD COMPOUNDS[1]

Compound	Formula	M.W.	S.G.	M.P.	Solubility, g/100 ml		
					Cold water	Hot water	Other solvents
Lead	Pb	207.19	11.35	327.5	i	i	sa
Acetate	$Pb(C_2H_3O_2)_2$	325.28	3.25	280	44.3	221^{50}	s glyc
Azide	$Pb(N_3)_2$	291.23	-	expl.	0.023	0.09^{70}	-
Bromate	$Pb(BrO_3)_2 \cdot H_2O$	481.02	5.53	d180	1.38	sl s	-
Bromide	$PbBr_2$	367.01	6.66	373	0.8441	4.71^{100}	sa
Carbonate	$PbCO_3$	267.20	6.6	d315	0.00011	d	sa,alk
Carbonate, basic	$2PbCO_3 \cdot Pb(OH)_2$	775.60	6.14	d400	i	i	s HNO_3
Chloride	$PbCl_2$	278.10	5.85	501	0.99	3.34^{100}	i al
Chlorobromide	PbClBr	322.56					
Chromate	$PbCrO_4$	323.18	6.12	844	$6x10^{-6}$	i	sa,alk
Chromate, basic	$PbCrO_4 \cdot PbO$	546.37	6.63		i	i	sa,alk
Cyanide	$Pb(CN)_2$	259.23			sl s	s	s KCN
Fluoride	PbF_2	245.19	8.24	855	0.064		s HNO_3
Fluorochloride	PbFCl	261.64	7.05	601	0.037	0.1081	
Formate	$Pb(CHO_2)_2$	297.23	4.63	d190	1.6	20	i al
Hydride	PbH_2	209.21		d			
Hydroxide	$Pb(OH)_2$	241.20		d145	0.0155	sl s	sa,alk
Iodate	$Pb(IO_3)_2$	557.00	6.155	d300	0.0012	0.003	s HNO_3
Iodide	PbI_2	461.00	6.16	402	0.063	0.41	s,alk
Nitrate	$Pb(NO_3)_2$	331.20	4.53	d470	37.65	127	s,alk

Table 3A-1. (continued). PHYSICAL PROPERTIES OF INORGANIC LEAD COMPOUNDS[1]

Compound	Formula	M.W.	S.G.	M.P.	Solubility, g/100 ml		
					Cold water	Hot water	Other solvents
Nitrate, basic	$Pb(OH)NO_3$	286.20	5.93	d180	19.4	s	sa
Oxalate	PbC_2O_4	295.21	5.28	d300	0.00016		sa
Oxide	PbO	223.19	9.53	888	0.0017		s,alk
Dioxide	PbO_2	239.19	9.375	d290	i	i	sa
Oxide (red)	Pb_3O_4	685.57	9.1	d500	i	i	sa
Phosphate	$Pb_3(PO_4)_2$	811.51	7	1014	$1.4x10^{-5}$	i	s,alk
Sulfate	$PbSO_4$	303.25	6.2	1170	0.00425	0.0056	
Sulfide	PbS	239.25	7.5	1114	$8.6x10^{-5}$		sa
Sulfite	$PbSO_3$	287.25		d	i	i	sa
Thiocyanate	$Pb(SCN)_2$	323.35	3.82	d190	0.05	0.2	s,alk

Abbreviations: a - acid; al - alcohol; alk - alkali; d - decomposes; expl - explodes; glyc - glycol; i - insoluble; s - soluble; M.W. - molecular weight; S.G. - specific gravity; and M.P. - melting point.

Source: Weast, 1975.

Table 3A-2. TEMPERATURE VARIATION OF THE VAPOR PRESSURES OF COMMON LEAD COMPOUNDS

Name	Formula	M.P.	Temperature °C					
			1 mm	10 mm	40 mm	100 mm	400 mm	760 mm
Lead	Pb	327.4	973	1162	1309	1421	1630	1744
Lead bromide	$PbBr_2$	373	513	610	686	745	856	914
Lead chloride	$PbCl_2$	501	547	648	725	784	893	954
Lead flouride	PbF_2	855	solid	904	1003	1080	1219	1293
Lead iodide	PbI_2	402	479	571	644	701	807	872
Lead oxide	PbO	890	943	1085	1189	1265	1402	1472
Lead sulfide	PbS	1114	852 (solid)	975 (solid)	1048 (solid)	1108 (solid)	1221	1281

Source: Stull, 1947

3A.2. THE CHELATE EFFECT

The stability constants of chelated complexes are normally several orders of magnitude higher than those of comparable monodentate complexes; this effect is called the chelate effect, and is very readily explained in terms of kinetic considerations. A comparison of the binding of a single bidentate ligand with that of two molecules of a chemically similar monodentate ligand shows that, for the monodentate case, the process can be represented by the equations:

$$M + B \underset{k_b}{\overset{k_a}{\rightleftharpoons}} M\text{-}B \qquad (3A\text{-}1)$$

$$M\text{-}B + B \underset{k_d}{\overset{k_c}{\rightleftharpoons}} MB_2 \qquad (3A\text{-}2)$$

The related expressions for the bidentate case are:

$$M + B\text{-}B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} M\text{-}B\text{-}B \qquad (3A\text{-}3)$$

$$M\text{-}B\text{-}B \underset{k^4}{\overset{k_3}{\rightleftharpoons}} M \begin{matrix} B \\ B \end{matrix} \qquad (3A\text{-}4)$$

The overall equilibrium constants, therefore, are:

$$K^1 = \frac{k_a k_c}{k_b k_d}; \qquad K_2 = \frac{k_1 k_3}{k_2 k_4}$$

For a given metal, M, and two ligands, B and B-B, which are chemically similar, it is established that k_1 and k_a have similar values to each other, as do k_2 and k_b and k_4 and k_d; each of these pairs of terms represents chemically similar processes. The origin of the chelate effect lies in the very large value of k_3 relative to that of k_c. This comes about because k_3 represents a unimolecular process, whereas k_c is a bimolecular rate constant. Consequently, $K_2 >> K_1$.

This concept can, of course, be extended to polydentate ligands; in general, the more extensive the chelation, the more stable the metal complex. Hence, one would anticipate, correctly, that polydentate chelating agents such as penicillamine or EDTA can form extremely stable complexes with metal ions.

3A.3 REFERENCES

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4. SAMPLING AND ANALYTICAL METHODS FOR ENVIRONMENTAL LEAD

4.1 INTRODUCTION

Lead, like all criteria pollutants, has a designated Reference Method for monitoring and analysis as required in State Implementation Plans for determining compliance with the lead National Ambient Air Quality Standard. The Reference Method [C.F.R. (1982) 40:§50] uses a high volume sampler (hi-vol) for sample collection and atomic absorption spectrometry for analysis. The reference method may be revised to require collection of a specific size fraction of atmospheric particles. Size specific inlets will be discussed in Section 4.2.3.

Airborne lead originates principally from man-made sources, about 75 to 90 percent from automobile exhaust, and is transported through the atmosphere to vegetation, soil, water, and animals. Knowledge of environmental concentrations of lead and the extent of its movement among various media is essential to control lead pollution and to assess its effects on human populations.

The collection and analysis of environmental samples for lead require a rigorous quality assurance program [C.F.R. (1982) 40:§58]. It is essential that the investigator recognize all sources of contamination and use every precaution to eliminate them. Contamination occurs on the surfaces of collection containers and devices, on the hands and clothing of the investigator, in the chemical reagents, in the laboratory atmosphere, and on the labware and tools used to prepare the sample for analysis. General procedures for controlling contamination in trace metal analysis are described by Zief and Mitchell (1976). Specific details for the analysis of lead are given in Patterson and Settle (1976). In the following discussion of methods for sampling and analysis, it is assumed that all procedures are normally carried out with precise attention to contamination control.

In the following sections, the specific operation, procedure and instrumentation involved in monitoring and analyzing environmental lead are discussed. Site selection criteria are treated briefly due to the lack of verifying data. Much remains to be done in establishing valid criteria for sampler location. The various types of samples and substrates used to collect airborne lead are described. Methods for collecting dry deposition, wet deposition, aqueous, soil and vegetation samples are also reviewed along with current sampling methods specific to mobile and stationary sources. Finally, advantages and limitations of techniques for sample preparation and analysis are discussed.

4.2 SAMPLING

The purpose of sampling is to determine the nature and concentration of lead in the environment. Sampling strategy is dictated by research needs. This strategy encompasses site selection, choice of instrument used to obtain representative samples, and choice of method used to preserve sample integrity. In the United States, sampling stations for air pollutants have been operated since the early 1950's. These early stations were a part of the National Air Surveillance Network (NASN), which has now become the National Filter Analysis Network (NFAN). Two other types of networks have been established to meet specific data requirements. State and Local Air Monitoring Stations (SLAMS) provide data from specific areas where pollutant concentrations and population densities are the greatest and where monitoring of compliance to standards is critical. The National Air Monitoring Station (NAMS) network is designed to serve national monitoring needs, including assessment of national ambient trends. SLAMS and NAMS stations are maintained by state and local agencies and the air samples are analyzed in their laboratories. Stations in the NFAN network are maintained by state and local agencies, but the samples are analyzed by laboratories in the U.S. Environmental Protection Agency, where quality control procedures are rigorously maintained.

Data from all three networks are combined into one data base, the National Aerometric Data Bank (NADB). These data may be individual chemical analyses of a 24-hour sampling period arithmetically averaged over a calendar period, or chemical composites of several filters used to determine a quarterly composite. Data are occasionally not available because they do not conform to strict statistical requirements. A summary of the data from the NADB appears in Section 7.2.1.

4.2.1 Regulatory Siting Criteria for Ambient Aerosol Samplers

In September of 1981, EPA promulgated regulations establishing ambient air monitoring and data reporting requirements for lead [C.F.R. (1982) 40:§58] comparable to those already established in May of 1979 for the other criteria pollutants. Whereas sampling for lead is accomplished when sampling for TSP, the designs of lead and TSP monitoring stations must be complementary to insure compliance with the NAMS criteria for each pollutant, as presented in Table 4-1, Table 4-2, and Figure 4-1.

In general, the criteria with respect to monitoring stations designate that there must be at least two SLAMS sites for lead in any area which has a population greater than 500,000 and/or any area where lead concentration currently exceeds the ambient lead standard (1.5 $\mu g/m^3$) or has exceeded it since January 1, 1974. In such areas, the SLAMS sites designated as part of the NAMS network must include a microscale or middlescale site located near a major roadway (≥30,000 ADT), as well as a neighborhood scale site located in a highly populated residential sector with high traffic density (≥30,000 ADT).

TABLE 4-1. DESIGN OF NATIONAL AIR MONITORING STATIONS

Criteria	TSP (Final Rule)	Air Pb (Final Rule)				
Stations required						
Spatial scale						
Category (a)	Neighborhood scale	Microscale or middle scale				
Category (b)	-	Neighborhood scale				
Number required	As per Table 4-2	Minimum 1 each category where population >500,000				
Siting						
Category (a)	High traffic and population density neighborhood scale	Major roadway microscale	or	Major roadway middle scale		
	>3000	≥30,000		≥10,000	20,000	≥40,000
Meters from edge of roadway	As per Figure 4-1	5-15		>15-50	>15-75	>15-100
meters above ground level	2-15	2-7		2-15	2-15	2-15
Category (b)		High traffic and population density neighborhood scale				
		≤10,000	20,000	≥40,000		
Meters from edge of roadway		>50	>75	>100		
Meters above ground level		2-15	2-15	2-15		

Source: C.F.R. (1982) 40:§58 App E

TABLE 4-2. TSP NAMS CRITERIA

Approximate Number of Stations Per Area			
	Concentration		
Population Category	High[1]	Medium[2]	Low[3]
High -- >500,000	6-8	4-6	0-2
Medium -- 100-500,000	4-6	2-4	0-2
Low -- 50-100,000	2-4	1-2	0

[1]When TSP Concentration exceeds by 20% Primary Ambient Air Standard of 75 $\mu g/m^3$ annual geometric mean.

[2]TSP Concentration > Secondary Ambient Air Standard of 60 $\mu g/m^3$ annual geometric mean.

[3]TSP Concentration < Secondary Ambient Air Standard.

Source: C.F.R. (1982) 40:§58 App D

With respect to the siting of monitors for lead and other criteria pollutants, there are standards for elevation of the monitors above ground level, setback from roadways, and setback from obstacles. A summary of the specific siting requirements for lead is presented in Table 4-1 and summarized below:

- Samples must be placed between 2 and 15 meters from the ground and greater than 20 meters from trees.
- Spacing of samplers from roads should vary with traffic volume; a range of 5 to 100 meters from the roadway is suggested.
- Distance from samplers to obstacles must be at least twice the height the obstacle protrudes above the sampler.
- There must be a 270° arc of unrestricted air flow around the monitor to include the prevailing wind direction that provides the maximum pollutant concentration to the monitor.
- No furnaces or incineration flues should be in close proximity to the monitor.

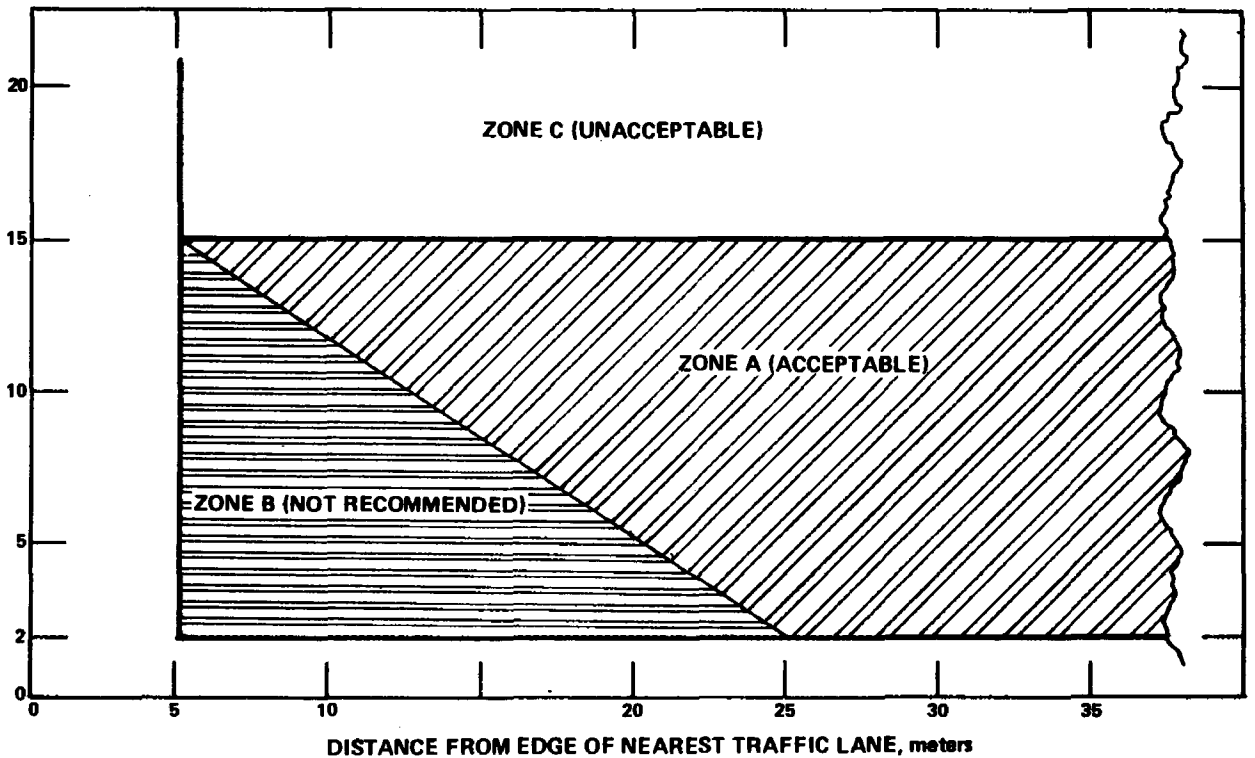

Figure 4-1. Acceptable zone for siting TSP monitors where the average daily traffic exceeds 3000 vehicles/day.

Zone A: Recommended for neighborhood, urban, regional and most middle spatial scales. All NAMS are in this zone.
Zone B: If SLAMS are placed in Zone B they have middle scale of representativeness.

Source: 46 FR 44159-44172

To clarify the relationship between monitoring objectives and the actual siting of a monitor, the concept of a spatial scale of representativeness was developed. The spatial scales are described in terms of the physical dimensions of the air space surrounding the monitor throughout which pollutant concentrations are fairly similar. Table 4-3 describes the scales of representativeness while Table 4-4 relates monitoring objectives to the appropriate spatial scale.

The time scale may also be an important factor. A study by Lynam (1972) illustrates the effect of setback distance on short-term (15 minute) measurements of lead concentrations directly downwind from the source. They found sharp reductions in lead concentration with increasing distance from the roadway. A similar study by PEDCo Environmental, Inc. (1981) did not show the same pronounced reduction when the data were averaged over monthly or quarterly time periods. The apparent reason for this effect is that windspeed and direction are not consistent. Therefore, siting criteria must include sampling times sufficiently long to include average windspeed and direction, or a sufficient number of samples must be collected over short sampling periods to provide an average value consistent with a 24-hour exposure.

4.2.2 Ambient Sampling for Particulate and Gaseous Lead

Airborne lead is primarily inorganic particulate matter but may occur in the form of organic gases. Devices used for collecting samples of ambient atmospheric lead include the standard hi-vol and a variety of other collectors employing filters, impactors, impingers, or scrubbers, either separately or in combination. Some samplers measure total particulate matter gravimetrically; thus the lead data are usually expressed in $\mu g/g$ PM or $\mu g/m^3$ air. Other samplers do not measure PM gravimetrically; therefore, the lead data can only be expressed as $\mu g/m^3$. Some samplers measure lead deposition expressed in $\mu g/cm^2$. Some instruments separate particles by size. As a general rule, particles smaller than 2.5 μm are defined as fine, and those larger than 2.5 μm are defined as coarse.

In a typical sampler, the ambient air is drawn down into the inlet and deposited on the collection surface after one or more stages of particle size separation. Inlet effectiveness, internal wall losses, and retention efficiency of the collection surface may bias the collected sample by selectively excluding particles of certain sizes.

4.2.2.1 High Volume Sampler (hi-vol). The present SLAMS and NAMS employ the standard hi-vol sampler (Robson and Foster, 1962; Silverman and Viles, 1948; U.S. Environmental Protection Agency, 1971) as part of their sampling networks. As a Federal Reference Method Sampler, the hi-vol operates with a specific flow rate range of 1.13 to 1.70 m^3/min, drawing air through a

TABLE 4-3. DESCRIPTION OF SPATIAL SCALES OF REPRESENTATIVENESS

Microscale	Defines ambient concentrations in air volumes associated with areas ranging from several to 100 meters in size.
Middle Scale	Defines concentrations in areas from 100 to 500 meters (area up to several city blocks).
Neighborhood Scale	Defines concentrations in an extended area of uniform land use, within a city, from 0.5 to 4.0 kilometers in size.
Urban Scale	Defines citywide concentrations, areas from 4-50 kilometers in size. Usually requires more than one site.
Regional Scale	Defines concentrations in a rural area with homogeneous geography. Range of tens to hundreds of kilometers.
National and Global Scales	Defines concentrations characterizing the U.S. and the globe as a whole.

Source: C.F.R. (1982) 40:§58 App. D

TABLE 4-4. RELATIONSHIP BETWEEN MONITORING OBJECTIVES AND APPROPRIATE SPATIAL SCALES

Monitoring objective	Appropriate spatial scale for siting air monitors
Highest Concentration	Micro, Middle, Neighborhood (sometimes Urban).
Population	Neighborhood, Urban
Source Impact	Micro, Middle, Neighborhood
General (Background)	Neighborhood, Regional

Source: C.F.R. (1982) 40:§58 App. D

200 x 250 mm glass fiber filter. At these flow rates, 1600 to 2500 m^3 of air per day are sampled. Many hi-vol systems are presently equipped with mass flow sensors to control the total flow rate through the filter.

The present hi-vol approach has been shown, during performance characterization tests, to have a number of deficiencies. First, wind tunnel testing by Wedding et al. (1977) has shown that the inlet characteristics of the hi-vol sampler are strongly affected by particle size, windspeed, and wind direction. However, since most lead particles have been shown to have a mass median diameter (MMD) in the range of 0.25 to 1.4 μm (Lee and Goranson, 1972), the hi-vol sampler should present reasonably good estimates of ambient lead concentrations. However, for particles greater than 5 μm, the hi-vol system is unlikely to collect representative samples (McFarland and Rodes, 1979; Wedding et al., 1977). In addition, Lee and Wagman (1966) and Stevens et al. (1978) have documented that the use of glass fiber filters leads to the formation of artifactual sulfate. Spicer et al. (1978) suggested a positive artifactual nitrate, while Stevens et al. (1980) showed both a positive and negative artifact may occur with glass or quartz filters when using a hi-vol sampler.

4.2.2.2 Dichotomous Sampler. The dichotomous sampler collects two particle size fractions, typically 0 to 2.5 μm and 2.5 μm to the upper cutoff of the inlet employed (normally 10 μm). The impetus for the dichotomy of collection, which approximately separates the fine and coarse particles, was provided by Whitby et al. (1972) to assist in the identification of particle sources. A 2.5 μm cutpoint for the separator was also recommended by Miller et al. (1979) because it satisfied the requirements of health researchers interested in respirable particles, provided adequate separation between two naturally occurring peaks in the size distribution, and was mechanically practical. Because the fine and coarse fractions collected in most locations tend to be acidic and basic, respectively, this separation also minimizes potential particle interaction after collection.

The particle separation principle used by this sampler was described by Hounam and Sherwood (1965) and Conner (1966). The version now in use by EPA was developed by Loo et al. (1979). The separation principle involves acceleration of the particles through a nozzle. Ninety percent of the flowstream is diverted to a small particle collector, while the larger particles continue by inertia toward the large particle collection surface. The inertial virtual impactor design causes 10 percent of the fine particles to be collected with the coarse particle fraction. Therefore, the mass of fine and coarse particles must be adjusted to allow for their cross contamination. This mass correction procedure has been described by Dzubay et al. (1982).

Teflon® membrane filters with pore sizes as large as 2.0 μm can be used in the dichotomous sampler (Dzubay et al, 1982; Stevens et al., 1980) and have been shown to have essentially 100 percent collection efficiency for particles with an aerodynamic diameter as small as 0.03 μm (Liu et al., 1976; See Section 4.2.5). Because the sampler operates at a flowrate of 1 m^3/hr (167 l/min) and collects sub-milligram quantities of particles, a microbalance with a 1 μg resolution is recommended for filter weighing (Shaw, 1980). Removal of the fine particles via this fractionation technique may result in some of the collected coarse particles falling off the filter if care is not taken during filter handling and shipping. However, Dzubay and Barbour (1983) have developed a filter coating procedure which eliminates particle loss during transport. A study by Wedding et al. (1980) has shown that the Sierra® inlet to the dichotomous sampler was sensitive to windspeed. The 50 percent cutpoint (D_{50}) was found to vary from 10 to 22 μm over the windspeed range of 0 to 15 km/hr.

Automated versions of the sampler allow timely and unattended changes of the sampler filters. Depending on atmospheric concentrations, short-term samples of as little as 4 hours can provide diurnal pattern information. The mass collected during such short sample periods, however, is extremely small and highly variable results may be expected.

4.2.2.3 Impactor Samplers. Impactors provide a means of dividing an ambient particle sample into subfractions of specific particle size for possible use in determining size distribution. A jet of air is directed toward a collection surface, which is often coated with an adhesive or grease to reduce particle bounce. Large, high-inertia particles are unable to turn with the airstream and consequently hit the collection surface. Smaller particles follow the airstream and are directed toward the next impactor stage or to the filter. Use of multiple stages, each with a different particle size cutpoint, provides collection of particles in several size ranges.

For determining particle mass, removable impaction surfaces may be weighed before and after exposure. The particles collected may be removed and analyzed for individual elements. The selection and preparation of these impaction surfaces have significant effects on the impactor performance. Improperly coated or overloaded surfaces can cause particle bounce to lower stages resulting in substantial cutpoint shifts (Dzubay et al., 1976). Additionally, coatings may cause contamination of the sample. Marple and Willeke (1976) showed the effect of various impactor substrates on the sharpness of the stage cutpoint. Glass fiber substrates can also cause particle bounce or particle interception (Dzubay et al., 1976) and are subject to the formation of artifacts, due to reactive gases interacting with the glass fiber, similar to those on hi-vol sampler filters (Stevens et al., 1978).

Cascade impactors typically have 2 to 10 stages, and flowrates for commercial low-volume versions range from about 0.01 to 0.10 m^3/min. Lee and Goranson (1972) modified a commercially available 0.03 m^3/min low-volume impactor and operated it at 0.14 m^3/min to obtain larger mass collections on each stage. Cascade impactors have also been designed to mount on a hi-vol sampler and operate at flowrates as high as 0.6 to 1.1 m^3/min.

Particle size cutpoints for each stage depend primarily on sampler geometry and flowrate. The smallest particle size cutpoint routinely used is approximately 0.3 μm, although special low-pressure impactors such as that described by Hering et al. (1978) are available with cutpoints as small as 0.05 μm. However, due to the low pressure, volatile organics and nitrates are lost during sampling. A membrane filter is typically used after the last stage to collect the remaining small particles.

4.2.2.4 Dry Deposition Sampling. Dry deposition may be measured directly with surrogate or natural surfaces, or indirectly using micrometeorological techniques. The earliest surrogate surfaces were dustfall buckets placed upright and exposed for several days. The HASL wet-dry collector is a modification which permits one of a pair of buckets to remain covered except during rainfall. These buckets do not collect a representative sample of particles in the small size range where lead is found because the rim perturbs the natural turbulent flow of the main airstream (Hicks et al., 1980). They are widely used for other pollutants, especially large particles, in the National Atmospheric Deposition Program.

Other surrogate surface devices with smaller rims or no rims have been developed recently (Elias et al., 1976; Lindberg et al., 1979; Peirson et al., 1973). Peirson et al. (1973) used horizontal sheets of filter paper exposed for several days with protection from rainfall. Elias et al. (1976) used Teflon® disks held rigid with a 1 cm Teflon® ring. Lindberg et al. (1979) used petri dishes suspended in a forest canopy. In all of these studies, the calculated deposition velocity (see Section 6.3.1) was within the range expected for small aerosol particles.

A few studies have measured direct deposition on vegetation surfaces using chemical washing techniques to remove surface particles. These determinations are generally 4 to 10 times lower than comparable surrogate surface measurements (Elias et al., 1976; Lindberg et al., 1979), but the reason for this difference could be that natural surfaces represent net accumulation rather than total deposition. Lead removed by rain or other processes would show an apparently lower deposition rate.

There are several micrometeorological techniques that have been used to measure particle deposition. They overcome the major deficiency of surrogate surfaces, the lack of correlation between the natural and artificial surfaces, but micrometeorological techniques require expensive equipment and skilled operators. They measure instantaneous or short-term deposition

only, and this deposition is inferred to be to a plane projected surface area only, not necessarily to vegetation surfaces.

Of the five micrometeorological techniques commonly used to measure particle deposition, only two have been used to measure lead particle deposition. Everett et al. (1979) used the profile gradient technique by which lead concentrations are measured at two or more levels within 10 m above the surface. Parallel meteorological data are used to calculate the net flux downward. Droppo (1980) used eddy correlation, which measures fluctuations in the vertical wind component with adjacent measurements of lead concentrations. The calculated differences of each can be used to determine the turbulent flux. These two micrometeorological techniques and the three not yet used for lead, modified Bowen, variance, and eddy accumulation, are described in detail in Hicks et al. (1980).

4.2.2.5 Gas Collection. When sampling ambient lead with systems employing filters, it is likely that vapor-phase organolead compounds will pass through the filter media. The use of bubblers downstream of the filter containing a suitable reagent or absorber for collection of these compounds has been shown to be effective (Purdue et al., 1973). Organolead may be collected on iodine crystals, adsorbed on activated charcoal, or absorbed in an iodine monochloride solution (Skogerboe et al., 1977b).

In one experiment, Purdue et al. (1973) operated two bubblers in series containing iodine monochloride solution. One hundred percent of the lead was recovered in the first bubbler. It should be noted, however, that the analytical detection sensitivity was poor. In general, use of bubblers limits the sample volume due to losses by evaporation and/or bubble carryover.

4.2.3 Source Sampling

Sources of lead include automobiles, smelters, coal-burning facilities, waste oil combustion, battery manufacturing plants, chemical processing plants, facilities for scrap processing, and welding and soldering operations (see Section 5.3.3). A potentially important secondary source is fugitive dust from mining operations and from soils contaminated with automotive emissions (Olson and Skogerboe, 1975). Chapter 5 contains a complete discussion of sources of lead emissions. The following sections discuss the sampling of stationary and mobile sources.

4.2.3.1 Stationary Sources. Sampling of stationary sources for lead requires the use of a sequence of samplers at the source of the effluent stream. Since lead in stack emissions may be present in a variety of physical and chemical forms, source sampling trains must be designed to trap and retain both gaseous and particulate lead. A sampling probe is inserted

directly in the stack or exhaust stream. In the tentative ASTM method for sampling for atmospheric lead, air is pulled through a 0.45 μm membrane filter and an activated carbon adsorption tube (American Society for Testing and Materials, 1975a). In a study of manual methods for measuring emission concentrations of lead and other toxic materials, Coulson et al. (1973), recommended use of a filter, a system of impingers, a metering system, and a pump.

4.2.3.2 Mobile Sources. Three principal procedures have been used to obtain samples of auto exhaust aerosols for subsequent analysis for lead compounds: a horizontal dilution tunnel, plastic sample collection bags and a low residence time proportional sampler. In each procedure, samples are air diluted to simulate roadside exposure conditions. In the most commonly used procedure, a large horizontal air dilution tube segregates fine combustion-derived particles from larger lead particles ablated from combustion chamber and exhaust deposits. In this procedure, hot exhaust is ducted into a 56-cm diameter, 12-m long, air dilution tunnel and mixed with filtered ambient air in a 10-cm diameter mixing baffle in a concurrent flow arrangement. Total exhaust and dilution airflow rate is 28 to 36 m^3/min, which produces a residence time of approximately 5 sec in the tunnel. At the downstream end of the tunnel, samples of the aerosol are obtained by means of isokinetic probes using filters or cascade impactors (Habibi, 1970).

In recent years, various configurations of the horizontal air dilution tunnel have been developed. Several dilution tunnels have been made of polyvinyl chloride with a diameter of 46 cm, but these are subject to wall losses due to charge effects (Gentel et al., 1973; Moran et al., 1972; Trayser et al., 1975). Such tunnels of varying lengths have been limited by exhaust temperatures to total flows above approximately 11 m^3/min. Similar tunnels have a centrifugal fan located upstream, rather than a positive displacement pump located downstream (Trayser et al., 1975). This geometry produces a slight positive pressure in the tunnel and expedites transfer of the aerosol to holding chambers for studies of aerosol growth. However, turbulence from the fan may affect the sampling efficiency. Since the total exhaust plus dilution airflow is not held constant in this system, potential errors can be reduced by maintaining a very high dilution air/exhaust flow ratio (Trayser et al., 1975).

There have also been a number of studies using total filtration of the exhaust stream to arrive at material balances for lead with rather low back-pressure metal filters in an air distribution tunnel (Habibi, 1973; Hirschler et al., 1957; Hirschler and Gilbert, 1964; Sampson and Springer, 1973). The cylindrical filtration unit used in these studies is better than 99 percent efficient in retaining lead particles (Habibi, 1973). Supporting data for lead balances generally confirm this conclusion (Kunz et al., 1975).

In the bag technique, auto emissions produced during simulated driving cycles are air-diluted and collected in a large plastic bag. The aerosol sample is passed through a filtration or impaction sampler prior to lead analysis (Ter Haar et al., 1972). This technique may result in errors of aerosol size analysis because of condensation of low vapor pressure organic substances onto the lead particles.

To minimize condensation problems, a third technique, a low residence time proportional sampling system, has been used. It is based on proportional sampling of raw exhaust, again diluted with ambient air followed by filtration or impaction (Ganley and Springer, 1974; Sampson and Springer, 1973). Since the sample flow must be a constant proportion of the total exhaust flow, this technique may be limited by the response time of the equipment to operating cycle phases that cause relatively small transients in the exhaust flow rate.

4.2.4 Sampling for Lead in Other Media

Other primary environmental media that may be affected by airborne lead include precipitation, surface water, soil, vegetation, and foodstuffs. The sampling plans and the sampling methodologies used in dealing with these media depend on the purpose of the experiments, the types of measurements to be carried out, and the analytical technique to be used. General approaches are given below in lieu of specific procedures associated with the numerous possible special situations.

4.2.4.1 Precipitation. The investigator should be aware that dry deposition occurs continuously, that lead at the start of a rain event is higher in concentration than at the end, and that rain striking the canopy of a forest may rinse dry deposition particles from the leaf surfaces. Rain collection systems should be designed to collect precipitation on an event basis and to collect sequential samples during the event. They should be tightly sealed from the atmosphere before and after sampling to prevent contamination from dry deposition, falling leaves, and flying insects. Samples should be acidified to pH 1 with nitric acid and refrigerated immediately after sampling. All collection and storage surfaces should be thoroughly cleaned and free of contamination.

Two automated systems have been in use for some time. The Sangamo Precipitation Collector, Type A, collects rain in a single bucket exposed at the beginning of the rain event (Samant and Vaidya, 1982). These authors reported no leaching of lead from the bucket into a solution of 0.3N HNO_3. A second sampler, described by Coscio et al. (1982), also remains covered between rain events; it can collect a sequence of eight samples during the period of rain and may be fitted with a refrigeration unit for sample cooling. No reports of lead analyses were given. Because neither system is widely used, their monitoring effectiveness has not been thoroughly evaluated.

4.2.4.2 Surface Water. Atmospheric lead may be dissolved in water as hydrated ions, chemical complexes, and soluble compounds, or it may be associated with suspended matter. Because the physicochemical form often influences environmental effects, there is a need to differentiate among the various chemical forms of lead. Complete differentiation among all such forms is a complex task that has not yet been fully accomplished. The most commonly used approach is to distinguish between dissolved and suspended forms of lead. All lead passing through a 0.45 μm membrane filter is operationally defined as dissolved, while that retained on the filter is defined as suspended (Kopp and McKee, 1979).

When sampling water bodies, flow dynamics should be considered in the context of the purpose for which the sample is collected. Water at the convergence point of two flowing streams, for example, may not be well mixed for several hundred meters. Similarly, the heavy metal concentrations above and below the thermocline of a lake may be very different. Thus, several samples should be selected in order to define the degree of horizontal or vertical variation. The final sampling plan should be based on the results of pilot studies. In cases where the average concentration is of primary concern, samples can be collected at several points and then mixed to obtain a composite.

Containers used for sample collection and storage should be fabricated from essentially lead-free plastic or glass, e.g., conventional polyethylene, Teflon®, or quartz. These containers must be leached with hot acid for several days to ensure minimum lead contamination (Patterson and Settle, 1976). If only the total lead is to be determined, the sample may be collected without filtration in the field. Nitric acid should be added immediately to reduce the pH to less than 2 (U.S. Environmental Protection Agency, 1978). The acid will normally dissolve the suspended lead. Otherwise, it is recommended that the sample be filtered upon collection to separate the suspended and dissolved lead and the latter preserved by acid addition as above. It is also recommended that water samples be stored at 4°C until analysis to avoid further leaching from the container wall (Fishman and Erdmann, 1973; Kopp and Kroner, 1967; Lovering, 1976; National Academy of Sciences, 1972; U.S. Environmental Protection Agency, 1978).

4.2.4.3 Soils. The distance and depth gradients associated with lead in soil from emission sources must be considered in designing the sampling plan. Beyond that, actual sampling is not particularly complex (Skogerboe et al., 1977b). Vegetation, litter, and large objects such as stones should not be included in the sample. Depth samples should be collected at 2 cm intervals to preserve vertical integrity. The samples should be air dried and stored in sealed containers until analyzed.

4.2.4.4 Vegetation. Because most soil lead is in forms unavailable to plants, and because lead is not easily transported by plants, roots typically contain very little lead and shoots even less (Zimdahl, 1976; Zimdahl and Koeppe, 1977). Before analysis, a decision must be made as to whether or not the plant material should be washed to remove surface contamination from dry deposition and soil particles. If the plants are sampled for total lead content (e.g., if they serve as animal food sources), they cannot be washed. If the effect of lead on internal plant processes is being studied, the plant samples should be washed. In either case, the decision must be made at the time of sampling, as washing cannot be effective after the plant materials have dried. Fresh plant samples cannot be stored for any length of time in a tightly closed container before washing because molds and enzymatic action may affect the distribution of lead on and in the plant tissues. Freshly picked leaves stored in sealed polyethylene bags at room temperature generally begin to decompose in a few days. Storage time may be increased to approximately 2 weeks by refrigeration.

After collection, plant samples should be dried as rapidly as possible to minimize chemical and biological changes. Samples that are to be stored for extended periods of time should be oven dried to arrest enzymatic reactions and render the plant tissue amenable to grinding. Storage in sealed containers is required after grinding. For analysis of surface lead, fresh, intact plant parts are agitated in dilute nitric acid or EDTA solutions for a few seconds.

4.2.4.5 Foodstuffs. From 1972 to 1978, lead analysis was included in the Food and Drug Administration Market Basket Survey, which involves nationwide sampling of foods representing the average diet of an 18-year-old male, i.e., the individual who on a statistical basis eats the greatest quantity of food (Kolbye et al., 1974). Various food items from the several food classes are purchased in local markets and made up into meal composites in the proportion that each food item is ingested; they are then cooked or otherwise prepared as they would be consumed. Foods are grouped into 12 food classes, then composited and analyzed chemically. Other sampling programs may be required for different investigative purposes. For those foods where lead may be deposited on the edible portion, the question of whether or not to use typical kitchen washing procedures before analysis should be considered in the context of the experimental purpose.

4.2.5 Filter Selection and Sample Preparation

In sampling for airborne lead, air is drawn through filter materials such as glass fiber, cellulose acetate, or porous plastic (Skogerboe et al., 1977b, Stern, 1968). These materials often include contaminant lead that can interfere with the subsequent analysis (Gandrud and Lazrus, 1972; Kometani et al. 1972; Luke et al., 1972; Seeley and Skogerboe, 1974). If the

sample collected is large, then the effects of these trace contaminants may be negligible (Witz and MacPhee, 1976). Procedures for cleaning filters to reduce the lead blank rely on washing with acids or complexing agents (Gandrud and Lazrus, 1972). The type of filter and the analytical method to be used often determines the ashing technique. In some methods, e.g., X-ray fluorescence, analysis can be performed directly on the filter if the filter material is suitable (Dzubay and Stevens, 1975). Skogerboe (1974) provided a general review of filter materials.

The main advantages of glass fiber filters are low pressure drop and high particle collection efficiency at high flow rates. The main disadvantage is variable lead blank, which makes their use inadvisable in many cases (Kometani et al., 1972; Luke at al., 1972). This has placed a high priority on the standardization of a suitable filter for hi-vol samples (Witz and MacPhee, 1976). Other investigations have indicated, however, that glass fiber filters are now available that do not present a lead interference problem (Scott et al., 1976b). Teflon® filters have been used since 1975 by Dzubay et al. (1982) and Stevens et al. (1978), who have shown these filters to have very low lead blanks (<2 ng/cm^2). The collection efficiencies of filters, and also of impactors, have been shown to be dominant factors in the quality of the derived data (Skogerboe et al., 1977a).

Sample preparation usually involves conversion to a solution through wet ashing of solids with acids or through dry ashing in a furnace followed by acid treatment. Either approach works effectively if used properly (Kometani et al., 1972; Skogerboe et al., 1977b). In one investigation of porous plastic Nuclepore® filters, some lead blanks were too high to allow measurements of ambient air lead concentrations (Skogerboe et al., 1977b).

4.3 ANALYSIS

The choice of analytical method depends on the nature of the data required, the type of sample being analyzed, the skill of the analyst, and the equipment available. For general determination of elemental lead, atomic absorption spectroscopy is widely used and recommended [40 C.F.R. (1982) 40:§50]. Optical emission spectrometry (Scott et al., 1976b) and X-ray fluorescence (Stevens et al., 1978) are rapid and inexpensive methods for multielemental analyses. X-ray fluorescence can measure lead concentrations reliably to 1 ng/m^3 using samples collected with commercial dichotomous samplers. Other analytical methods have specific advantages appropriate for special studies. Only those analytical techniques receiving widespread current use in lead analysis are described below. More complete reviews are available in the literature (American Public Health Association, 1971; Lovering, 1976; Skogerboe et al., 1977b; National Academy of Sciences, 1980).

With respect to measuring lead without sampling or laboratory contamination, several investigators have shown that the magnitude of the problem is quite large (Patterson and Settle, 1976; Patterson et al., 1976; Pierce et al., 1976; Patterson, 1982; Skogerboe, 1982). It appears that the problem may be caused by failure to control the blank or by failure to standardize instrument operation (Patterson, 1982; Skogerboe, 1982). The laboratory atmosphere, collecting containers, and the labware used may be primary contributors to the lead blank problem (Murphy, 1976; Patterson, 1982; Skogerboe, 1982). Failure to recognize these and other sources such as reagents and hand contact is very likely to result in the generation of artificially high analytical results. Samples with less than 100 µg Pb should be analyzed in a clean laboratory especially designed for the elimination of lead contamination. Moody (1982) has described the construction and application of such a laboratory at the National Bureau of Standards.

For many analytical techniques, a preconcentration step is recommended. Leyden and Wegschelder (1981) have described several procedures and the associated problems with controlling the analytical blank. There are two steps to preconcentration. The first is the removal of organic matter by dry ashing or wet digestion. The second is the separation of lead from interfering metallic elements by coprecipitation or passing through a resin column. New separation techniques are continuously being evaluated, many of which have application to specific analytical problems. Yang and Yeh (1982) have described a polyacrylamide-hydrous-zirconia (PHZ) composite ion exchanger suitable for high phosphate solutions. Corsini, et al. (1982) evaluated a macroreticular acrylic ester resin capable of removing free and inorganically bound metal ions directly from aqueous solution without prior chelation.

4.3.1 Atomic Absorption Spectroscopy (AAS)

Atomic absorption spectroscopy (AAS) is a widely accepted method for the measurement of lead in environmental sampling (Skogerboe et al., 1977b). A variety of lead studies using AAS have been reported (Kometani et al., 1972; Zoller et al., 1974; Huntzicker et al., 1975; Scott et al., 1976b; Lester et al., 1977; Hirao et al., 1979; Compton and Thomas, 1980; Bertenshaw and Gelsthorpe, 1981).

The lead atoms in the sample must be vaporized either in a precisely controlled flame or in a furnace. Furnace systems in AAS offer high sensitivity as well as the ability to analyze small samples (Lester et al., 1977; Rouseff and Ting, 1980; Stein et al., 1980; Bertenshaw et al., 1981). These enhanced capabilities are offset in part by greater difficulty in analytical calibration and by loss of analytical precision.

Pachuta and Love (1980) collected particles on cellulose acetate filters. Disks (0.5 cm^2) were punched from these filters and analyzed by insertion of the nichrome cups containing the disks into a flame. Another application involves the use of graphite cups as particle filters with the subsequent analysis of the cups directly in the furnace system (Seeley and Skogerboe, 1974; Torsi et al., 1981). These two procedures offer the ability to determine particulate lead directly with minimal sample handling.

In an analysis using AAS and hi-vol samplers, atmospheric concentrations of lead were found to be 0.076 ng/m^3 at the South Pole (Maenhaut et al., 1979). Lead analyses of 995 particulate samples from the NASN were accomplished by AAS with an indicated precision of 11 percent (Scott et al., 1976a, see also Section 7.2.1.1). More specialized AAS methods for the determination of tetraalkyl lead compounds in water and fish tissue have been described by Chau et al. (1979) and in air by Birnie and Noden (1980) as well as Rohbock et al. (1980).

Atomic absorption requires as much care as other techniques to obtain highly precise data. Background absorption, chemical interference, background light loss, and other factors can cause errors. A major problem with AAS is that untrained operators use it in many laboratories without adequate quality control.

Techniques for AAS are still evolving. An alternative to the graphite furnace, evaluated by Jin and Taga (1982), uses a heated quartz tube through which the metal ion in gaseous hydride form flows continuously. Sensitivities were 1 to 3 ng/g for lead. The technique is similar to the hydride generators used for mercury, arsenic, and selenium. Other nonflame atomization systems, electrodeless discharge lamps, and other equipment refinements and technique developments have been reported (Horlick, 1982).

4.3.2 Emission Spectroscopy

Optical emission spectroscopy is based on the measurement of the light emitted by elements when they are excited in an appropriate energy medium. The technique has been used to determine the lead content of soils, rocks, and minerals at the 5 to 10 µg/g level with a relative standard deviation of 5 to 10 percent (Anonymous, 1963); this method has also been applied to the analysis of a large number of air samples (Scott et al., 1976b; Sugimae and Skogerboe, 1978). The primary advantage of this method is that it allows simultaneous measurement of a large number of elements in a small sample (Ward and Fishman, 1976).

In a study of environmental contamination by automotive lead, sampling times were shortened by using a sampling technique in which lead-free porous graphite was used both as the filter medium and as the electrode in the spectrometer (Copeland et al., 1973; Seeley and Skogerboe, 1974). Lead concentrations of 1 to 10 $µg/m^3$ were detected after a half-hour flow at 800 to 1200 ml/min through the filter.

Scott et al. (1976a) analyzed composited particulate samples obtained with hi-vols for about 24 elements, including lead, using a direct reading emission spectrometer. Over 1000 samples collected by the NASN in 1970 were analyzed. Careful consideration of accuracy and precision led to the conclusion that optical emission spectroscopy is a rapid and practical technique for particle analysis.

More recent activities have focused attention on the inductively coupled plasma (ICP) system as a valuable means of excitation and analysis (Garbarino and Taylor, 1979; Winge et al., 1977). The ICP system offers a higher degree of sensitivity with less analytical interference than is typical of many of the other emission spectroscopic systems. Optical emission methods are inefficient when used for analysis of a single element, since the equipment is expensive and a high level of operator training is required. This problem is largely offset when analysis for several elements is required as is often the case for atmospheric aerosols.

4.3.3 X-Ray Fluorescence (XRF)

X-ray emissions that characterize the elemental content of a sample also occur when atoms are irradiated at sufficient energy to excite an inner-shell electron (Hammerle and Pierson, 1975; Jaklevic et al., 1973; Skogerboe et al., 1977b; Stevens et al., 1978). This fluorescence allows simultaneous identification of a range of elements including lead.

X-ray fluorescence may require a high-energy irradiation source. But with the X-ray tubes coupled with fluorescers (Jaklevic et al., 1973; Dzubay and Stevens, 1975; Paciga and Jervis, 1976) very little energy is transmitted to the sample, thus sample degradation is kept to a minimum (Shaw et al., 1980). Electron beams (McKinley et al., 1966), and radioactive isotope sources (Kneip and Laurer 1972) have been used extensively (Birks et al., 1971; Birks, 1972) as energy sources for XRF analysis. To reduce background interference, secondary fluorescers have been employed (Birks et al., 1971; Dzubay and Stevens, 1975). The fluorescent X-ray emission from the sample may be analyzed with a crystal monochromator and detected with scintillation or proportional counters (Skogerboe et al., 1977b) or with low-temperature semiconductor detectors that discriminate the energy of the fluorescence. The latter technique requires a very low level of excitation (Dzubay and Stevens, 1975; Toussaint and Boniforti, 1979).

X-ray emission induced by charged-particle excitation (proton-induced X-ray emission or PIXE) offers an attractive alterative to the more common techniques (Barfoot et al., 1979; Hardy et al., 1976; Johansson et al., 1970). Recognition of the potential of heavy-particle

bombardment for excitation was demonstrated by Johansson et al. (1970), who reported an interference-free signal in the picogram (10^{-12} g) range. The excellent capability of accelerator beams for X-ray emission analysis is partially due to the relatively low background radiation associated with the excitation. The high particle fluxes obtainable from accelerators also contribute to the sensitivity of the PIXE method. Literature reviews (Folkmann et al., 1974; Gilfrich et al., 1973; Herman et al., 1973; Walter et al., 1974) on approaches to X-ray elemental analysis agree that protons of a few MeV energy provide a preferred combination for high sensitivity analysis under conditions less subject to matrix interference effects. As a result of this premise, a system designed for routine analysis has been described (Johansson et al., 1975) and papers involving the use of PIXE for aerosol analysis have appeared (Hardy et al., 1976; Johansson et al., 1975). The use of radionuclides to excite X-ray fluorescence and to determine lead in airborne particles has also been described (Havranek and Bumbalova, 1981; Havranek et al., 1980).

X-radiation is the basis of the electron microprobe method of analysis. When an intense electron beam is incident on a sample, it produces several forms of radiation, including X-rays, whose wavelengths depend on the elements present in the material and whose intensities depend on the relative quantities of these elements. An electron beam that gives a spot size as small as 0.2 μm is possible. The microprobe is often incorporated in a scanning electron microscope that allows precise location of the beam and comparison of the sample morphology with its elemental composition. Under ideal conditions, the analysis is quantitative, with an accuracy of a few percent. The mass of the analyzed element may range from 10^{-14} to 10^{-16} g (McKinley et al., 1966).

Electron microprobe analysis is not a widely applicable monitoring method. It requires expensive equipment, complex sample preparation procedures, and a highly trained operator. The method is unique, however, in providing compositional information on individual lead particles, thus permitting the study of dynamic chemical changes and perhaps allowing improved source identification.

Advantages of X-ray fluorescence methods include the ability to detect a variety of elements, the ability to analyze with little or no sample preparation, low detection limits (2 ng Pb/m^3) and the availability of automated analytical equipment. Disadvantages are that the X-ray analysis requires liquid nitrogen (e.g., for energy-dispersive models) and highly trained analysts. The detection limit for lead is approximately 9 ng/cm^2 of filter area (Jaklevic and Walter, 1977), which is well below the quantity obtained in normal sampling periods with the dichotomous sampler (Dzubay and Stevens, 1975).

4.3.4 Mass Spectrometry

Isotope dilution mass spectrometry (IDMS) is an absolute measurement technique. It serves as the standard to which other analytical techniques are compared. No other techniques serve more reliably as a comparative reference. Its use for analyses at subnanogram concentrations of lead and in a variety of sample types has been reported (Chow et al., 1969, 1974; Facchetti and Geiss, 1982; Hirao and Patterson, 1974; Murozumi et al., 1969; Patterson et al., 1976; Rabinowitz et al., 1973).

The isotopic composition of lead peculiar to various ore bodies and crustal sources may also be used as a means of tracing the origin of anthropogenic lead. Other examples of IDMS application are found in several reports cited above, and in Rabinowitz and Wetherill (1972), Stacey and Kramers (1975), and Machlan et al. (1976).

4.3.5 Colorimetric Analysis

Colorimetric or spectrophotometric analysis for lead using dithizone (diphenylthiocarbazone) as the reagent has been used for many years (Anonymous, 1963; Horowitz et al., 1970; Sandell, 1944). It was the primary method recommended by a National Academy of Sciences (1972) report on lead, and the basis for the tentative method of testing for lead in the atmosphere by the American Society for Testing and Materials (1975b). Prior to the development of the IDMS method, colorimetric analysis served as the reference by which other methods were tested.

The procedures for the colorimetric analysis require a skilled analyst if reliable results are to be obtained. The ASTM conducted a collaborative test of the method (Foster et al., 1975) and concluded that the procedure gave satisfactory precision in the determination of particulate lead in the atmosphere. In addition, the required apparatus is simple and relatively inexpensive, the absorption is linearly related to the lead concentration, large samples can be used, and interferences can be removed (Skogerboe et al., 1977b). Realization of these advantages depends on meticulous attention to the procedures and reagents.

4.3.6 Electrochemical Methods: Anodic Stripping Voltammetry (ASV), Differential Pulse Polarography (DPP)

Analytical methods based on electrochemical phenomena are found in a variety of forms (Sawyer and Roberts, 1974; Willard et al., 1974). They are characterized by a high degree of sensitivity, selectivity, and accuracy derived from the relationship between current, charge, potential, and time for electrolytic reactions in solutions. The electrochemistry of lead is based primarily on Pb(II), which behaves reversibly in ionic solutions having a reduction potential near -0.4 volt versus the standard calomel electrode (Skogerboe et al., 1977b). Two

electrochemical methods generally offer sufficient analytical sensitivity for most lead measurement problems. Differential pulse polarography (DPP) relies on the measurement of the faradaic current for lead as the voltage is scanned while compensating for the nonfaradaic (background) current produced (McDonnell, 1981). Anodic stripping voltammetry (ASV) is a two step process in which the lead is preconcentrated onto a mercury electrode by an extended but selected period of reduction. After the reduction step, the potential is scanned either linearly or by differential pulse to oxidize the lead and allow measurement of the oxidation (stripping) current. The preconcentration step allows development of enhanced analytical signals; when used in combination with the differential pulse method lead concentrations at the subnanogram level can be measured (Florence, 1980).

The ASV method has been widely applied to the analysis of atmospheric lead (Harrison et al., 1971; Khandekar et al., 1981; MacLeod and Lee, 1973). Landy (1980) has shown the applicability to the determination of Cd, Cu, Pb, and Zn in Antarctic snow while Nguyen et al. (1979) have analyzed rain water and snow samples. Green et al. (1981) have used the method to determine Cd, Cu, and Pb in sea water. The ASV determination of Cd, Cu, Pb, and Zn in foods has been described by Jones et al., 1977; Mannino, 1982; and Satzger et al., 1982, and the general accuracy of the method summarized by Holak (1980). Current practice with commercially available equipment allows lead analysis at subnanogram concentrations with precision at the 5 to 10 percent on a routine basis (Skogerboe et al., 1977b). New developments center around the use of microcomputers in controlling the stripping voltage (Kryger, 1981) and conformational modifications of the electrode (Brihaye and Duyckaerts, 1982).

4.3.7 Methods for Compound Analysis

The majority of analytical methods are restricted to measurement of total lead and cannot directly identify the various compounds of lead. The electron microprobe and other X-ray fluorescence methods provide approximate data on compounds on the basis of the ratios of elements present (Ter Haar and Bayard, 1971). Gas chromatography (GC) using the electron capture detector has been demonstrated to be useful for organolead compounds (Shapiro and Frey, 1968). The use of atomic absorption as the GC detector for organolead compounds has been described by DeJonghe et al. (1981), while a plasma emission detector has been used by Estes et al. (1981). In addition, Messman and Rains (1981) have used liquid chromatography with an atomic absorption detector to measure organolead compounds. Mass spectrometry may also be used with gas chromatography (Mykytiuk et al., 1980).

Powder X-ray diffraction techniques have been applied to the identification of lead compounds in soils by Olson and Skogerboe (1975) and by Linton et al. (1980). X-ray diffraction techniques were used (Harrison and Perry, 1977; Foster and Lott, 1980; Jacklevic et al., 1981) to identify lead compounds collected on air filters.

4.4 CONCLUSIONS

To monitor lead particles in air, collection with the hi-vol and dichotomous samplers and analysis by atomic absorption spectrometry and X-ray fluorescence methods have emerged as the most widely used methods. Sampling with the hi-vol has inherent biases in sampling large particles and does not provide for fractionation of the particles according to size, nor does it allow determination of the gaseous (organic) concentrations. Sampling with a dichotomous sampler provides size information but does not allow for gaseous lead measurements. The size distribution of lead aerosol particles is important in considering inhalable particulate matter. To determine gaseous lead, it is necessary to back up the filter with chemical scrubbers such as a crystalline iodine trap.

X-ray fluorescence and optical emission spectroscopy are applicable to multi-element analysis. Other analytical techniques find application for specific purposes. The paucity of data on the types of lead compounds at subnanogram levels in the ambient air is currently being addressed through development of improved XRF analyzer procedures.

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5. SOURCES AND EMISSIONS

5.1 HISTORICAL PERSPECTIVE

The history of global lead emissions has been assembled from chronological records of deposition in polar snow strata, marine and freshwater sediments, and the annual rings of trees. These records are important for two reasons. They aid in establishing natural background levels of lead in air, soils, plants, animals, and humans. They also place current trends in atmospheric lead concentrations in the perspective of historical changes. Most chronological records document the sudden increase in atmospheric lead at the time of the industrial revolution, and a later burst during the 1920's when lead-alkyls were first added to gasoline.

Tree ring analyses are not likely to show the detailed year-by-year chronological record of atmospheric lead increases. In situations where ring porous tree species that retain the nutrient solution only in the most recent annual rings are growing in heavily polluted areas where soil lead has increased 100-fold, significant increases in the lead content of tree rings over the last several decades have been documented. Rolfe (1974) found 4-fold increases in both rural and urban tree rings using pooled samples from the period of 1910-20 compared to samples from the period from 1963-73. Symeonides (1979) found a 2-fold increase during a comparable interval at a high lead site but no increase at a low lead site. Baes and Ragsdale (1981) found significant post-1930 increases in oak (Quercus) and hickory (Carya) with high lead exposure, but only in hickory with low lead exposure.

Pond sediment analyses (Shirahata, et al. 1980) have shown a 20-fold increase in lead deposition during the last 150 years (Figure 5-1), documenting not only the increasing use of lead since the beginning of the industrial revolution in western United States, but also the relative fraction of natural vs. anthropogenic lead inputs. Other studies have shown the same magnitude of increasing deposition in freshwater sediments (Christensen and Chien, 1981; Galloway and Likens, 1979; Edgington and Robbins, 1976), and marine sediments (Ng and Patterson, 1982). The pond and marine sediments also document the shift in isotopic composition caused by the recent opening of the New Lead Belt in Missouri, where the ore body has an isotopic composition substantially different from other ore bodies of the world.

Perhaps the best and certainly the most controversial chronological record is that of the polar ice strata of Murozumi et al. (1969), which extends nearly three thousand years back in time (Figure 5-1). The data of Jaworowski et al. (1981) and Herron et al. (1977) do not agree with the value found by Murozumi et al. (1969) for the early period around 800 B.C. Ng and Patterson (1981) have shown that the ice cores of Herron et al. (1977) were contaminated with

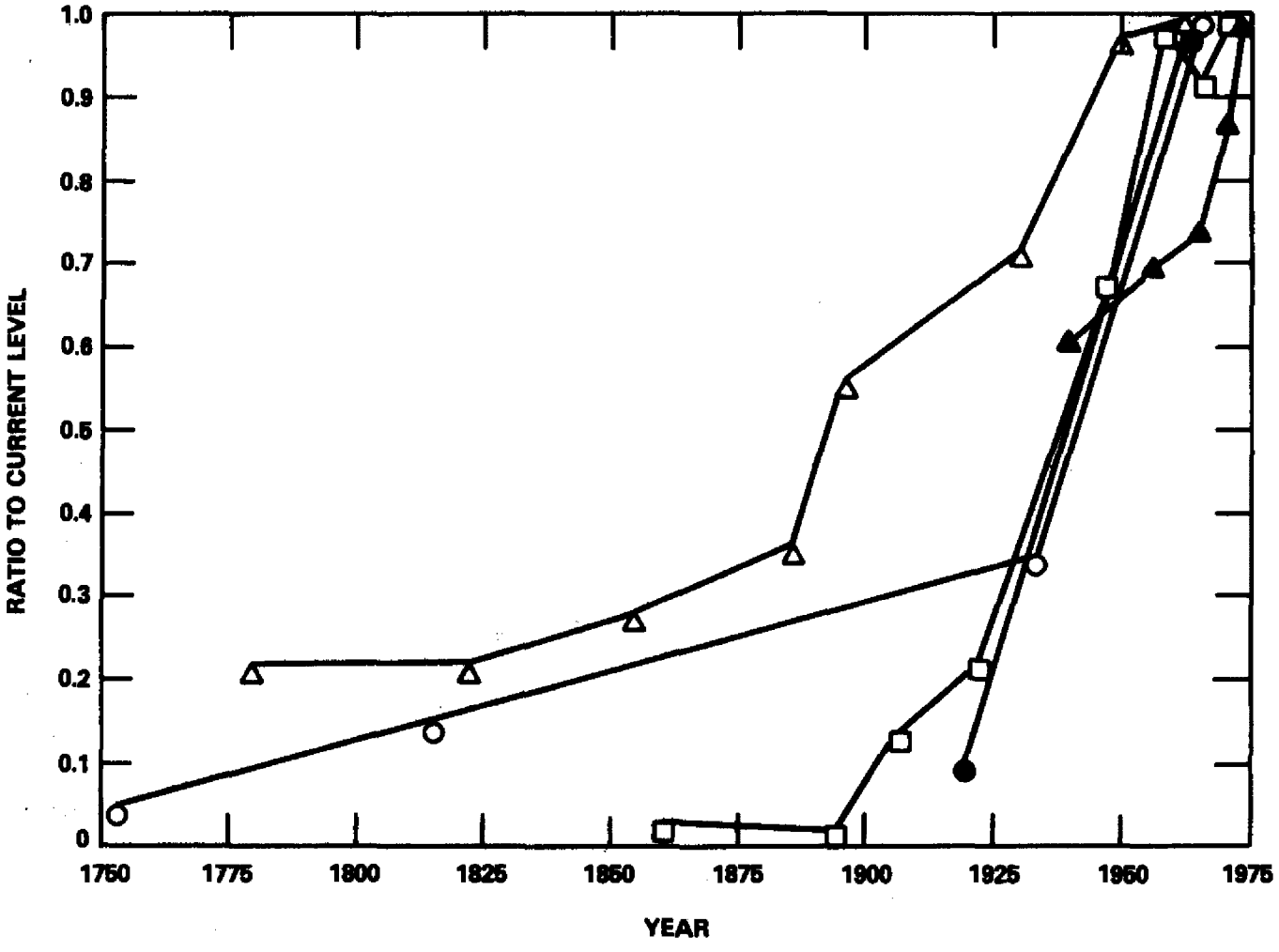

Figure 5-1. Chronological record of the relative increase of lead in snow strata, pond and lake sediments, marine sediments, and tree rings. The data are expressed as a ratio of the latest year of the record and should not be interpreted to extend back in time to natural or uncontaminated levels of lead concentration.

Source: Adapted from Murozumi et al. (1969) (○), Shirahata et al. (1980) (□), Edgington and Robbins (1976) (△), Ny and Patterson (1979) (▲), and Rolfe (1974) (●).

industrial greases. Patterson (1983) has also discussed the probable errors made by Jaworowski et al. (1981) in their determination of manmade lead in glacial ice samples. At the South Pole, Boutron (1982) observed a 4-fold increase of lead in snow from 1957 to 1977 but saw no increase during the period 1927 to 1957. The observed increase was attributed to global rather than local or regional pollution. The author suggested the extensive atmospheric lead pollution which began in the 1920's did not reach the South Pole until the mid-1950's. This interpretation agrees with that of Maenhaut et al. (1979), who found atmospheric concentrations of lead of 0.000076 $\mu g/m^3$ at the same location. This concentration is about 3-fold higher than the 0.000024 $\mu g/m^3$ estimated by Patterson (1980) and Servant (1982) to be the natural lead concentration in the atmosphere. In summary, it is likely that atmospheric lead emissions have increased 2000-fold since the pre-Roman era, that even at this early time the atmosphere may have been contaminated by a factor of three over natural levels (Murozumi et al. 1969), and that global atmospheric concentrations have increased dramatically since the 1920's.

The history of global emissions may also be determined from total production of lead, if the fraction of that lead released to the atmosphere during the smelting process, the fraction released during industrial consumption and the amount of lead emitted from non-lead sources are known. The historical picture of lead production has been pieced together from many sources by Settle and Patterson (1980) (Figure 5-2). They used records of accumulated silver stocks to estimate the lead production needed to support coin production. Until the industrial revolution, lead production was determined largely by the ability or desire to mine lead for its silver content. Since that time, lead has been used as an industrial product in its own right, and efforts to improve smelter efficiency, including control of stack emissions and fugitive dusts, have made lead production more economical. This improved efficiency is not reflected in the chronological record because of atmospheric emissions of lead from many other anthropogenic sources, especially gasoline combustion (see Section 5.3.3). From this knowledge of the chronological record, it is possible to sort out contemporary anthropogenic emissions from natural sources of atmospheric lead.

5.2 NATURAL SOURCES

Lead enters the biosphere from lead-bearing minerals in the lithosphere through both natural and man-made processes. Measurements of soil materials taken at 20-cm depths in the continental United States (Lovering, 1976; Shacklette et al. 1971) show a median lead concentration of 15 to 16 μg Pb/g soil. Ninety-five percent of these measurements show 30 $\mu g/g$ of lead or less, with a maximum sample concentration of 700 $\mu g/g$.

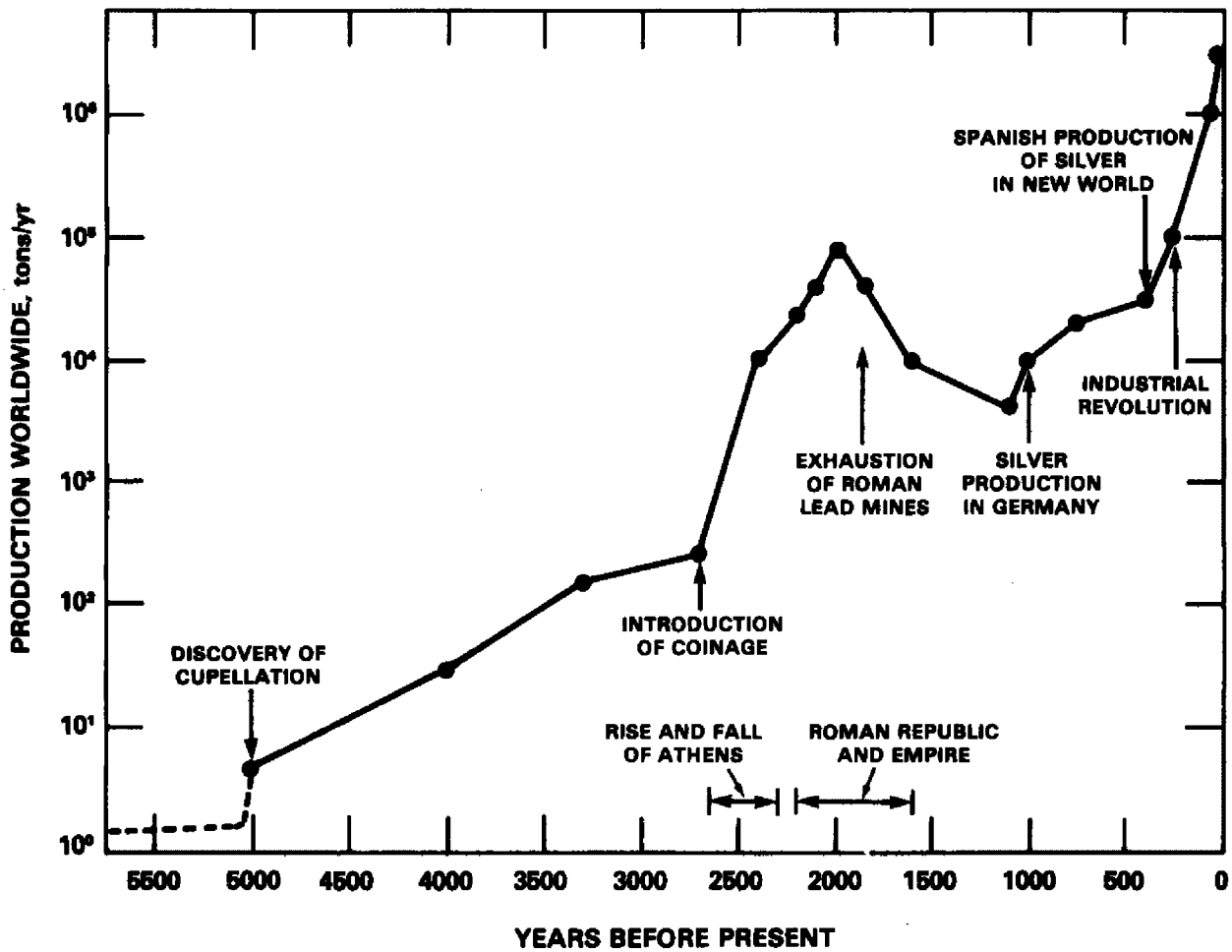

Figure 5-2. The global lead production has changed historically in response to major economic and political events. Increases in lead production (note log scale) correspond approximately to historical increases in lead emissions shown in Figure 5-1.

Source: Adapted from Settle and Patterson (1980).

In natural processes, lead is first incorporated in soil in the active root zone, from which it may be absorbed by plants, leached into surface waters, or eroded into windborne dusts (National Academy of Sciences, 1980; Chamberlain, 1970; Patterson, 1965; Chow and Patterson, 1962).

Natural emissions of lead from volcanoes have been estimated by Nriagu (1979) to be 6400 t/year based on enrichment over crustal abundance. That is, 10 X 10^9 kg/year of volcanic dust are produced, with an average concentration of 640 µg/g, or 40 times the crustal abundance of 16 µg/g. The enrichment factor is based on Lepel et al. (1978), who measured lead in the

plume of the Augustine volcano in Alaska. Settle and Patterson (1980) have calculated emissions of only 1 t/year, based on a measured Pb/S ratio of 1×10^{-7} and estimated sulfur emissions of 6 X 10 t/year. This measured Pb/S ratio was from volcanoes reported by Buat-Menard and Arnold (1978), and is likely to be a better estimate of lead emissions from volcanoes.

Calculations of natural contributions using geochemical information indicate that natural sources contribute a relatively small amount of lead to the atmosphere. For example, if the typical 25 to 40 $\mu g/m^3$ of rural airborne particulate matter consisted solely of wind-entrained soils containing 15 $\mu g/g$, and rarely more than 30 μg of lead/g, as cited above, then the natural contribution to airborne lead would range from 0.0004 to 0.0012 $\mu g/m^3$. It has been estimated from geochemical evidence that the natural particulate lead level is less than 0.0005 $\mu g/m^3$ (National Academy of Sciences, 1980; United Kingdom Department of the Environment, 1974). In fact, levels as low as 0.000076 $\mu g/m^3$ have been measured at the South Pole in Anarctica (Maenhaut et al., 1979). In contrast, average lead concentrations in urban suspended particulate matter range as high as 6 $\mu g/m^3$ (Akland, 1976; U.S. Environmental Protection Agency, 1979, 1978). Evidently, most of this urban particulate lead stems from man-made sources.

5.3 MANMADE SOURCES

5.3.1 Production

Lead occupies an important position in the U.S. economy, ranking fifth among all metals in tonnage used. Approximately 85 percent of the primary lead produced in this country is from native mines, although often associated with minor amounts of zinc, cadmium, copper, bismuth, gold, silver, and other minerals (U.S. Bureau of Mines, 1975). Missouri lead ore deposits account for approximately 80 to 90 percent of the domestic production. Approximately 40 to 50 percent of annual lead production is recovered and eventually recycled.

5.3.2 Utilization

The 1971-1980 uses of lead are listed by major product category in Table 5-1 (U.S. Bureau of Mines, 1972-1982). Total utilization averaged approximately 1.36×10^6 t/yr over the 10-year period, with storage batteries and gasoline additives accounting for ~70 percent of total use. The gasoline antiknocks listed in Table 5-1 include additives for both domestic and import markets. The additive fraction of total lead utilization has decreased from greater than 18 percent in 1971-1973 to less than 9.5 percent in 1981. Certain products, especially batteries, cables, plumbing, weights, and ballast, contain lead that is economically recoverable as secondary lead. This reserve of lead in use is estimated at 3.8 million metric

TABLE 5-1. U.S. UTILIZATION OF LEAD BY PRODUCT CATEGORY (1971-1981), METRIC TONS/YEAR
(U.S. BUREAU OF MINES, 1981, 1982)

Product category	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981
Storage batteries	616,581	661,740	697,888	772,656	634,368	746,085	858,099	879,274	814,332	645,357	770,152
Gasoline antiknock additives[a]	239,666	252,545	248,890	227,847	189,369	217,508	211,296	178,473	186,945	127,903	111,367
Pigments and ceramics	73,701	80,917	98,651	105,405	71,718	95,792	90,704	91,642	90,790	78,430	80,165
Ammunition	79,423	76,822	73,091	78,991	68,098	66,659	62,043	55,776	53,236	48,662	49,514
Solder	63,502	64,659	65,095	60,116	52,011	57,448	58,320	68,390	54,278	41,366	29,705
Cable coverings	47,998	41,659	39,006	39,387	20,044	14,452	13,705	13,851	16,393	13,408	12,072
Caulking lead	27,204	20,392	18,192	17,903	12,966	11,317	8,725	9,909	8,017	5,684	5,522
Pipe and sheet lead	41,523	37,592	40,529	34,238	35,456	34,680	30,861	23,105	27,618	28,393	28,184
Type metal	18,876	18,089	19,883	18,608	14,703	13,614	11,395	10,795	10,019	8,997	7,838
Brass and bronze	18,180	17,963	20,621	20,172	12,157	14,207	15,148	16,502	18,748	13,981	13,306
Bearing metals	14,771	14,435	14,201	13,250	11,051	11,851	10,873	9,510	9,630	7,808	6,922
Other	56,958	63,124	61,019	62,106	54,524	68,181	64,328	75,517	68,329	50,314	52,354
TOTAL	1,298,383	1,349,846	1,397,876	1,450,679	1,176,465	1,351,794	1,435,497	1,432,744	1,358,335	1,070,303	1,167,101

[a]Includes additives for both domestic and export markets.

tons, of which only 0.5 to 0.8 million metric tons are recovered annually. Lead in pigments, gasoline additives, ammunition, foil, solder, and steel products is widely dispersed and therefore is largely unrecoverable.

5.3.3 Emissions

Lead or its compounds may enter the environment at any point during mining, smelting, processing, use, recycling, or disposal. Estimates of the dispersal of lead emissions into the environment by principal sources indicate that the atmosphere is the major initial recipient. Estimated lead emissions to the atmosphere are shown in Table 5-2. Mobile and stationary sources of lead emissions, although found throughout the nation, tend to be concentrated in areas of high population density, with the exception of smelters. Figure 5-3 shows the approximate locations of major lead mines, primary and secondary smelters and refineries, and alkyl lead plants (International Lead Zinc Research Organization, 1982).

5.3.3.1 Mobile Sources. The majority of lead compounds found in the atmosphere result from leaded gasoline combustion. Several reports indicate that transportation sources, which include light-duty, heavy-duty, and off-highway vehicles, contribute over 80 percent of the total atmospheric lead (Nationwide [lead] emissions report, 1980, 1979; U.S. Environmental Protection Agency, 1977). Other mobile sources, including aviation use of leaded gasoline and diesel and jet fuel combustion, contribute insignificant lead emissions to the atmosphere. The detailed emissions inventory in Table 5-2 shows that 86 percent of the lead emissions in the United States are from gasoline combustion. Cass and McRae (1983) assembled emissions inventory data on the Los Angeles Basin and determined that 83 percent of the fine particle emissions originated from highway vehicles. Lead is added to gasoline as an antiknock additive to enhance engine performance in the form of two tetralkyl lead compounds, tetraethyl and tetramethyl lead (see Section 3.4). Lead is emitted from vehicles primarily in the form of inorganic particles, although a very small fraction (<10 percent) of lead emissions are released as volatile organic compounds, i.e., lead alkyls (National Academy of Sciences, 1972).

The factors which affect both the rate of particulate lead emissions and the physicochemical properties of the emissions are: lead content of the fuel, other additives, vehicle fuel economy, the driving speed or conditions, and type of vehicle, as well as design parameters, maintenance, ages of the engine, exhaust, and emission control systems. The major types of vehicles are light-duty (predominantly cars) and heavy-duty (trucks and buses). The important properties of the particulate emissions include the total amount emitted, the size distribution of the particles, and the chemical composition of these particles as a function of particle size. The most commonly used index of particle size is the mass median equivalent

TABLE 5-2. ESTIMATED ATMOSPHERIC LEAD EMISSIONS FOR THE UNITED STATES, 1981, AND THE WORLD

Source category	Annual U.S. emissions (t/yr)	Percentage of U.S. total emissions	Annual global emissions (t/yr)
Gasoline combustion	35,000	85.9%	273,000
Waste oil combustion	830	2.0	8,900
Solid waste disposal	319	0.8	
Coal combustion	950	2.3	14,000
Oil combustion	226	0.6	6,000
Wood combustion	--	--	4,500
Gray iron production	295	0.7	50,000
Iron and steel production	533	1.3	
Secondary lead smelting	631	1.5	770
Primary copper smelting	30	0.1	27,000
Ore crushing and grinding	326	0.8	8,200
Primary lead smelting	921	2.3	31,000
Other metallurgical	54	0.1	
Zn smelting			16,000
Ni smelting			2,500
Lead alkyl manufacture	245	0.6	
Type metal	85	0.2	7,400
Portland cement production	71	0.2	
Miscellaneous	233	0.5	5,900
Total	40,739[a]	100%	449,170

[a]Inventory does not include emissions from exhausting workroom air, burning of lead-painted surfaces, welding of lead-painted steel structures, or weathering of painted surfaces.

Source: For U.S. emissions, Battye (1983), for global emissions, Nriagu (1979).

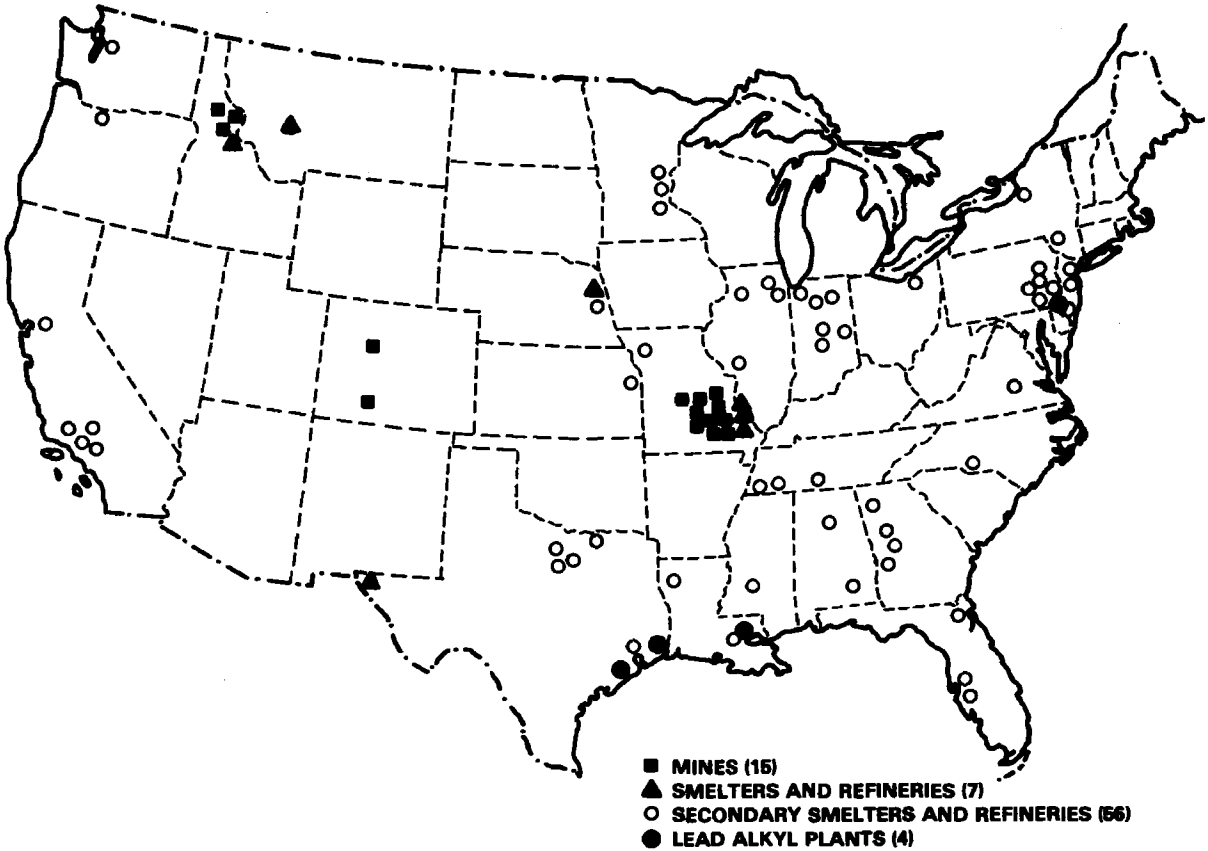

Figure 5-3. Locations of major lead operations in the United States.

Source: International Lead Zinc Research Organization (1982).

diameter (MMED), which is defined as the point in the size distribution of particles such that half the mass lies on either side of the MMED value (National Air Pollution Control Administration, 1970). Table 5-3 summarizes a recent study estimating the particulate emission rates and particle composition for light-duty vehicles operated on a leaded fuel of 1.8 g Pb/gallon (Hare and Black, 1981). Table 5-4 estimates particulate emission rates for heavy-duty vehicles (trucks) operated on a leaded fuel of 1.8 g Pb/gallon (Hare and Black, 1981). The lead content of 1.8 g Pb/gallon was chosen to approximate the lead concentration of leaded gasoline during 1979 (Table 5-5). Another recent study utilizing similar composite emission factors provides estimates of motor vehicle lead emissions for large areas (Provenzano, 1978).

Lead occurs, on the average, as PbBrCl in fresh exhaust particles (Hirschler et al., 1957). This lead compound is 64.2 percent lead by mass and is a common form of lead emitted due to the presence of the scavengers ethylene dichloride and ethylene dibromide in normal leaded fuel. PbBrCl has theoretical mass ratios for lead, bromine, and chlorine of 0.64, 0.25, and 0.11, respectively. The particle compositional data in Table 5-3 indicate that mass ratios for lead, bromine, and chlorine are approximately 0.60, 0.30, and 0.10, respectively, from both pre- and post-1970 vehicles. Data from another study (Lang et al., 1981), involving 1970-1979 vehicles, indicated that mass ratios for lead, bromine, and chlorine were 0.62, 0.30, and 0.08, respectively.

The fate of emitted lead particles depends upon their particle size (see Section 6.3.1). Particles initially formed by condensation of lead compounds in the combustion gases are quite small (well under 0.1 μm in diameter) (Pierson and Brachaczek, 1982). Particles in this size category are subject to growth by coagulation and, when airborne, can remain suspended in the atmosphere for 7 to 30 days and travel thousands of miles from their original source (Chamberlain et al., 1979). Larger particles are formed as the result of agglomeration of smaller condensation particles and have limited atmospheric lifetimes (Harrison and Laxen, 1981). The largest vehicle-emitted particles, which are greater than 100 μm in diameter, may be formed by materials flaking off from the surfaces of the exhaust system. As indicated in Table 5-3, the estimated mass median equivalent diameter of leaded particles from light-duty vehicles is <0.25 μm, suggesting that such particles have relatively long atmospheric lifetimes and the potential for long-distance transport. Similar values for MMED in automobile exhausts were found in Britain (0.27 μm) (Chamberlain et al. 1979) and Italy (0.33 μm) (Facchetti and Geiss, 1982). Particles this small deposit by Brownian diffusion and are generally independent of gravitation.

The size distribution of lead exhaust particles is essentially bimodal (Pierson and Brachaczek, 1976) and depends on a number of factors, including the particular driving pattern in which the vehicle is used and its past driving history (Ganley and Springer, 1974; Habibi,

TABLE 5-3. LIGHT-DUTY VEHICULAR PARTICULATE EMISSIONS*

Rate or property	Data by vehicle category: Pre-1970	Data by vehicle category: 1970 & later without catalyst
Exhaust particulate emissions, g/mi	0.29	0.13
Particle mass median equivalent diameter, μm	<0.25	<0.25
Percent of particulate mass as:		
Lead (Pb)	22 or greater	36 or greater
Bromine (Br)	11 or greater	18 or greater
Chlorine (Cl)	4 or greater	6 or greater
Trace metals	1	1 or greater
Carbon (C), total	33 or greater	33 or less
Sulfate ($SO_4^=$)	1.3	1.3 or greater
Soluble organics	~30 or less	~10

*Rate estimates are based on 1.8 Pb/gal fuel.

Source: Hare and Black (1981).

TABLE 5-4. HEAVY-DUTY VEHICULAR PARTICULATE EMISSIONS*

Heavy-duty category	Particulate emissions by model year: Pre-1970	Particulate emissions by model year: 1970 and later
Medium-duty trucks (6,000 to 10,000 lb GVW)	0.50	0.40
Heavy-duty trucks (over 10,000 lb GVW)	0.76	0.60

*Rate estimates are based on 1.8 g Pb/gal fuel, units are g/mi.

Source: Hare and Black (1981).

TABLE 5-5. RECENT AND PROJECTED CONSUMPTION OF GASOLINE LEAD

Calendar year	Gasoline volume (billions of gallons) Total	Leaded	Average lead content (g/gal) Sales weighted total pool	Leaded	Total lead (10^3t) 0.5 gpg pooled std	1.1 gpg leaded std	Air-lead ($\mu g/m^3$)[d]
1975[a]	102.3	92.5	1.62	1.81	165.6	---	1.23
1976	107.0	87.0	1.60	1.97	171.0	---	1.22
1977	113.2	79.7	1.49	2.12	168.7	---	1.20
1978	115.8	75.0	1.32	2.04	153.3	---	1.13
1979	111.2	68.1	1.16	1.90	129.5	---	0.93
1980	110.8	57.5	0.71	1.37	78.5	---	0.60
1981	102.6	51.0	0.59	1.19	61.0	---	0.47[c]
1982	100.0	40.6	0.64	1.44	62.0	---	0.45[c]
1983[b]	96.1	41.7			48.1	47.0	
1984	92.3	35.4	0.50	1.10	46.1	39.0	
1985	89.2	29.7	0.50	1.10	44.6	32.7	
1986	86.1	25.3	0.50	1.10	43.0	27.8	
1987	83.8	22.1	0.50	1.10	41.9	24.3	
1988	81.5	19.5	0.50	1.10	40.7	21.4	
1989	79.2	17.0	0.50	1.10	39.6	18.7	
1990	77.7	14.7	0.50	1.10	38.8	16.2	

[a]Data for the years 1975-1982 are taken from U.S. Environmental Protection Agency (1983b), in which data for 1975-1981 are actual consumption of lead and for 1982, estimates of consumption.

[b]Data for 1983-1990 are estimates taken from F.R. (1982 October 29).

[c]Estimated (this work)

[d]Data from Hunt and Neligan (1982), discussed in Chapter 7, are the maximum quarterly average lead levels from a composite of sampling sites.

1973; 1970; Ter Haar et al., 1972; Hirschler and Gilbert, 1964; Hirschler et al., 1957). As an overall average, it has been estimated that during the lifetime of the vehicle, approximately 35 percent of the lead contained in the gasoline burned by the vehicle will be emitted as small particles (<0.25 μm MMED), and approximately 40 percent will be emitted as larger particles (>10 μm MMED) (Ter Haar et al., 1972). The remainder of the lead consumed in gasoline combustion is deposited in the engine and exhaust system. Engine deposits are, in part, gradually transferred to the lubricating oil and removed from the vehicle when the oil is changed. A flow chart depicting lead-only emissions per gallon of fuel charged into the engine is shown in Figure 5-4. It is estimated that 10 percent of the lead consumed during combustion is released into the environment via disposal of used lubricating oil (Piver, 1977). In addition, some of the lead deposited in the exhaust system gradually flakes off, is emitted in the exhaust as extremely large particles, and rapidly falls into the streets and roads where it is incorporated into the dust and washed into sewers or onto adjacent soil.

Although the majority (>90 percent on a mass basis) of vehicular lead compounds are emitted as inorganic particles (e.g., PbBrCl), some organolead vapors (e.g., lead alkyls) are also emitted. The largest volume of organolead vapors arises from the manufacture, transport, and handling of leaded gasoline. Such vapors are photoreactive, and their presence in local atmospheres is transitory, i.e., the estimated atmospheric half-lives of lead alkyls, under typical summertime conditions, are less than half a day (Nielsen, 1982). Organolead vapors are most likely to occur in occupational settings (e.g., gasoline transport and handling operations, gas stations, parking garages) and have been found to contribute less than 10 percent of the total lead present in the atmosphere (Gibson and Farmer, 1981; National Academy of Sciences, 1972).

The use of lead additives in gasoline, which increased in volume for many years, is now decreasing as automobiles designed to use unleaded fuel constitute the major portion of the automotive population (Table 5-1). The decline in the use of leaded fuel is the result of two regulations promulgated by the U.S. Environmental Protection Agency (F.R., 1973 December 6). The first required the availability of unleaded fuel for use in automobiles designed to meet federal emission standards with lead-sensitive emission control devices (e.g., catalytic converters); the second required a reduction or phase-down of the lead content in leaded gasoline. Compliance with the phase-down of lead in gasoline has recently been the subject of proposed rulemakings. The final action (F.R., 1982 October 29) replaced the present 0.5 g/gal standard for the average lead content of all gasoline with a two-tiered standard for the lead content of leaded gasoline. Under this proposed rule, large refineries would be required to meet a standard of 1.10 g/gal for leaded gasoline while certain small refiners would be subject to a 1.90 g/gal standard until July 1, 1983, at which time they were made subject to the 1.10 g/gal standard.

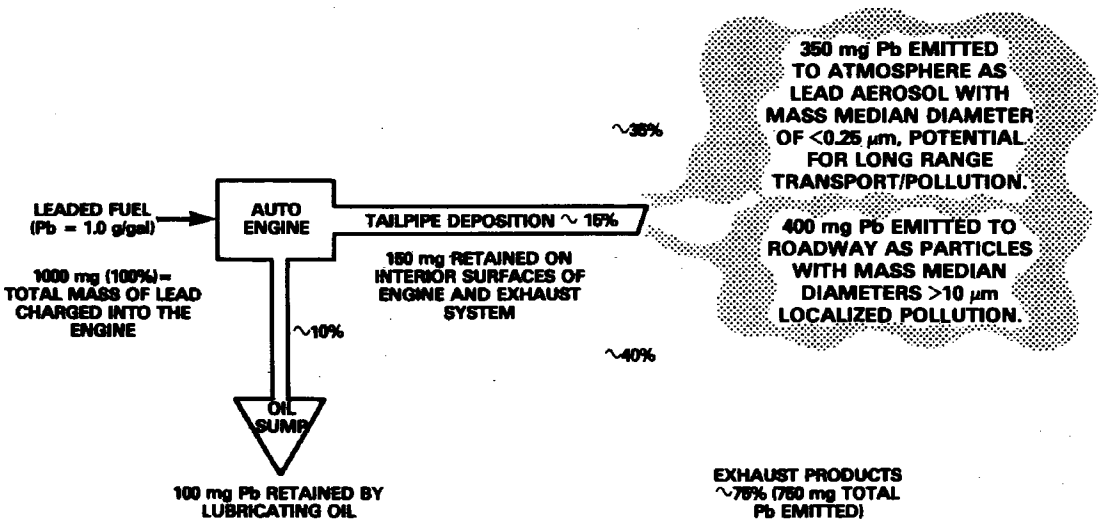

Figure 5-4. Estimated lead-only emissions distribution per gallon of combusted fuel.

The trend in lead content for U.S. gasolines is shown in Figure 5-5 and Table 5-5. Of the total gasoline pool, which includes both leaded and unleaded fuels, the average lead content has decreased 63 percent, from an average of 1.62 g/gal in 1975 to 0.60 g/gal in 1981 (Table 5-5, Figure 5-5). Accompanying the phase-down of lead in leaded fuel has been the increased consumption of unleaded fuel, from 11 percent of the total gasoline pool in 1975 to 50 percent in 1981 (Table 5-5 and Figure 5-6). Since 1975, when the catalytic converter was introduced by automobile manufacturers for automotive exhaust emissions control, virtually all new passenger cars have been certified on unleaded gasoline (with the exception of a few diesels and a very few leaded-gasoline vehicles). Because of the yearly turnover rate in the vehicle fleet, the demand for unleaded gasoline is forecast to increase to 58 percent of the total gasoline pool in 1982 and ~75 percent by 1985. As the demand for unleaded fuel increases, it may become uneconomical to distribute leaded gasoline for light-duty vehicles in low-volume localities.

The lead content of leaded gasoline (Table 5-5) is forecast to increase from 1.19 to 1.44 g/gal in 1982 (DuPont de Nemours, 1982). The reason for this increase is that under the 1982 0.5 g/gal total pool standard, refiners could add ever-increasing amounts of lead to each gallon of leaded gasoline (up to the level at which it would no longer be economically justified) as the amount of unleaded gasoline produced by the refinery increases. Thus, as the amount of unleaded gasoline increased, the amount of lead in leaded gasoline could also increase under the former regulations. The recent EPA decision (F.R., 1982 October 29) eliminated this practice, thereby ensuring that the amount of lead used in gasoline will decline after 1982 to 1.1 g/gal. Further decreases in lead emissions from gasoline combustion will depend on continued reductions in the sales of leaded gasoline.

Data describing the lead consumed in gasoline and average ambient lead levels (composite of maximum quarterly values) versus calendar year are listed in Table 5-5 and plotted in Figure 5-7. The 1975 through 1979 composite quarterly lead averages are based on 105 lead-monitoring sites, primarily urban. The 1980 composite average is based on 58 sites with valid annual data. The EPA National Aerometric Data Base is still receiving the 1980 data. The linear correlation (Figure 5-8) between lead consumed in gasoline and the composite maximum average quarterly ambient average lead level is very good with $r^2 = 0.99$. The 1981 and 1982 composite averages shown in Table 5-5 and Figures 5-7 and 5-8 are derived using the linear equation of Figure 5-6. Between 1975 and 1980, the lead consumed in gasoline decreased 52 percent (from 165,577 metric tons to 78,679 metric tons) while the corresponding composite maximum quarterly average of ambient lead decreased 51 percent (from 1.23 $\mu g/m^3$ to 0.60 $\mu g/m^3$). This indicates that control of lead in gasoline over the past several years has effected a direct decrease in peak ambient lead concentrations, at least for this group of monitoring sites.

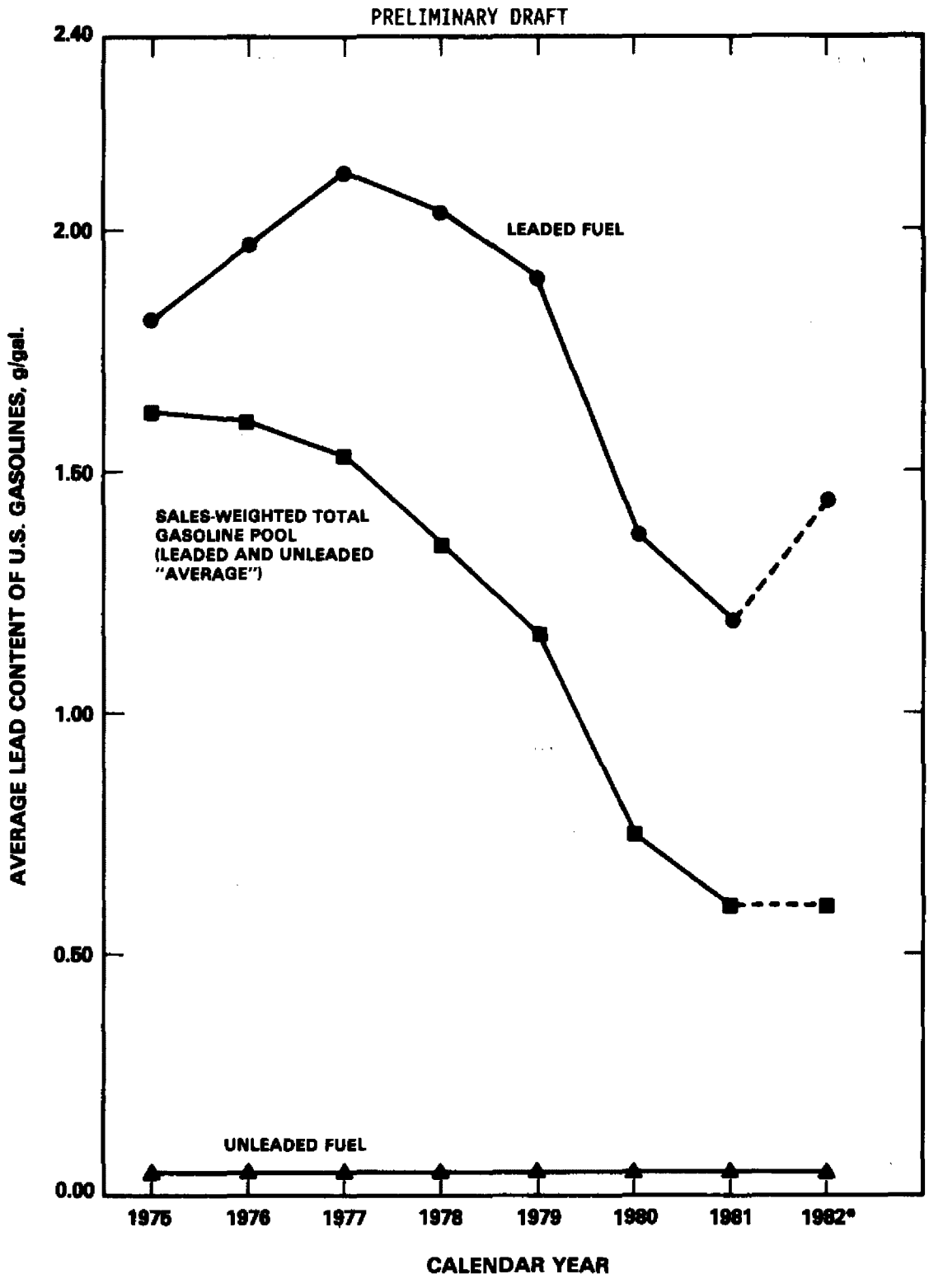

Figure 5-5. Trend in lead content of U.S. gasolines, 1975-1982. (DuPont, 1982).

***1982 DATA ARE FORECASTS.**

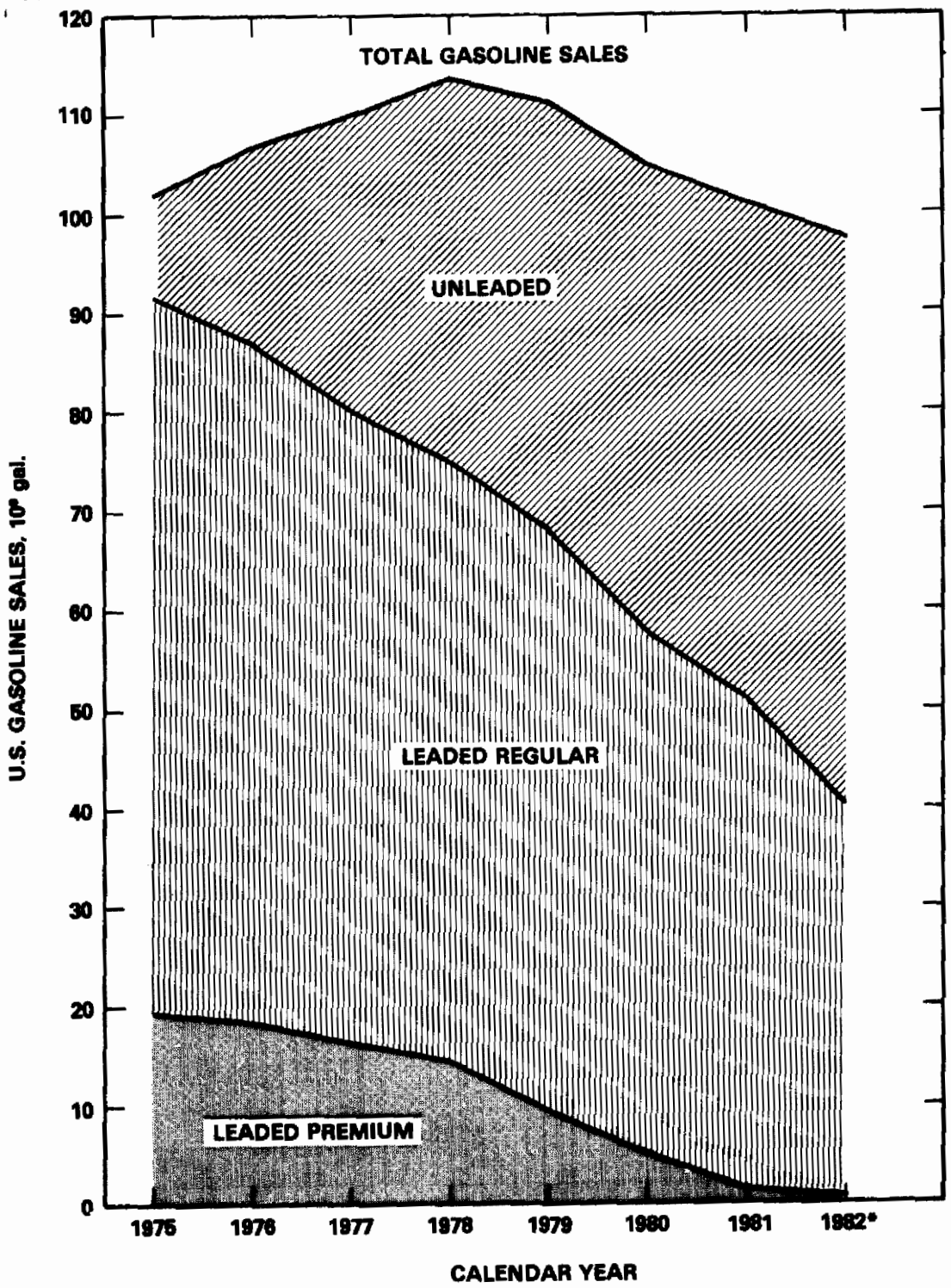

Figure 5-6. Trend in U.S. gasoline sales, 1975-1982. (DuPont, 1982).
***1982 DATA ARE FORECASTS.**

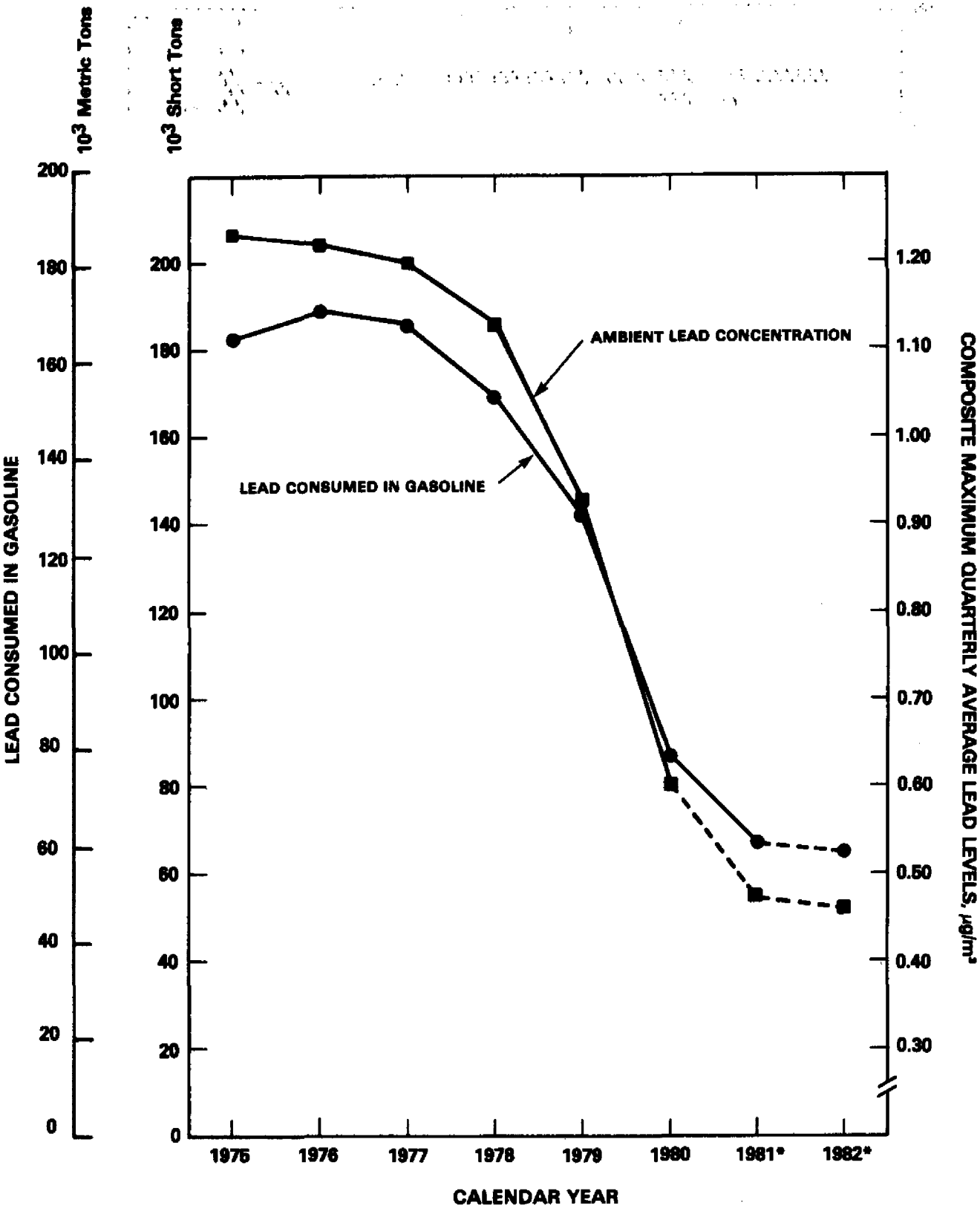

Figure 5-7. Lead consumed in gasoline (Du Pont, 1982) and ambient lead concentrations, 1975-1982. (Hunt and Neligan, 1982).
***DASHED LINES ARE ESTIMATES.**

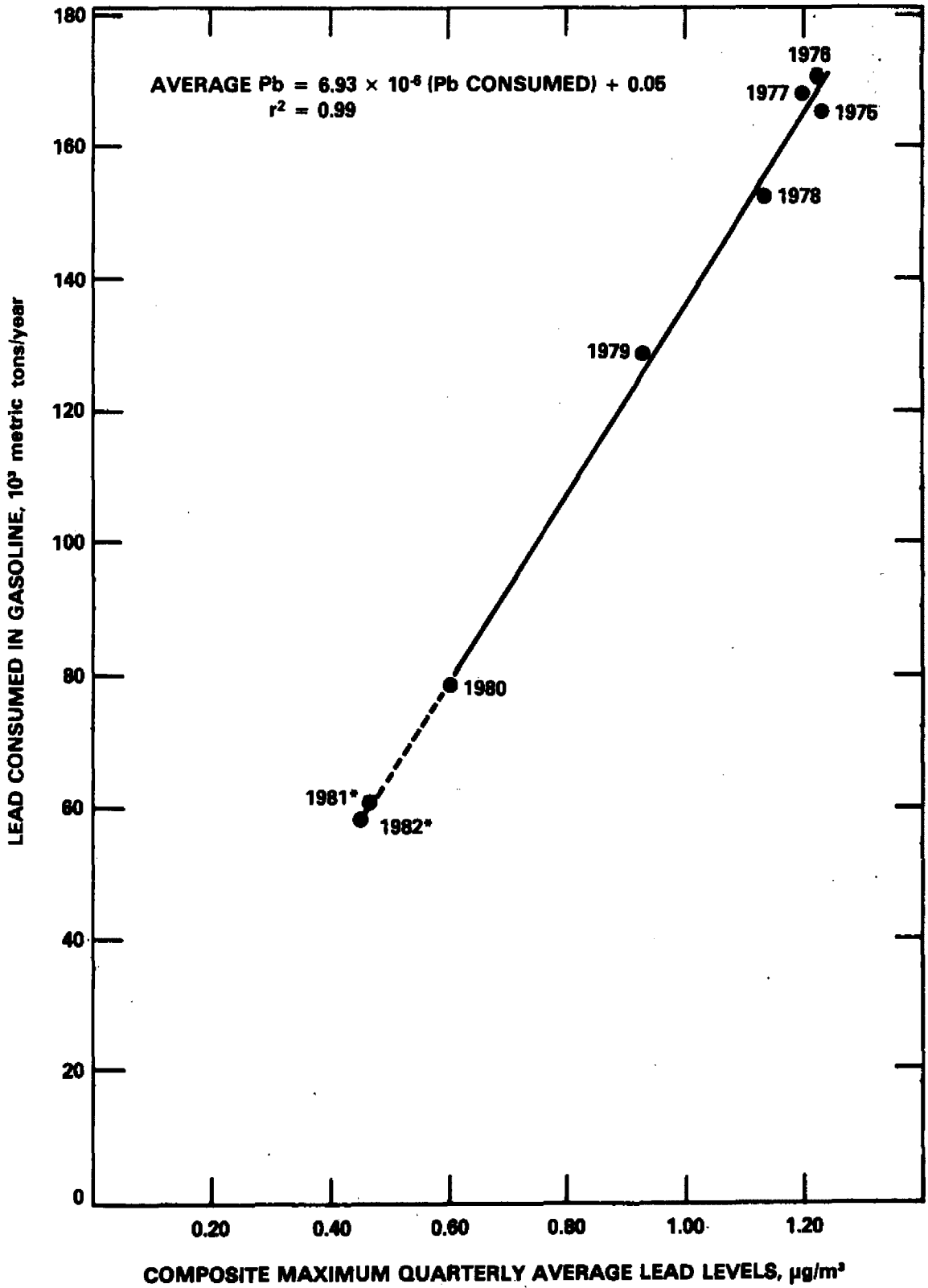

Figure 5-8. Relationship between lead consumed in gasoline and composite maximum quarterly average lead levels, 1975-1980.

***1981 AND 1982 DATA ARE ESTIMATES.**

Furthermore, the equation in Figure 5-8 implies that the complete elimination of lead from gasoline might reduce the composite average of the maximum quarterly lead concentrations at these stations to 0.05 $\mu g/m^3$, a level typical of concentrations reported for nonurban stations in the U.S. (see Chapter 7). Even this level of 0.05 $\mu g/m^3$ is regarded as evidence of human activity since it is at least two orders of magnitude higher than estimates of geochemical background lead concentrations discussed in Section 5.2.

5.3.3.2 Stationary Sources. As shown in Table 5-2 (based on 1982 emission estimates), solid waste incineration and combustion of waste oil are the principal contributors of lead emissions from stationary sources, accounting for two-thirds of stationary source emissions. The manufacture of consumer products such as lead glass, storage batteries, and lead additives for gasoline also contributes significantly to stationary source lead emissions. Since 1970, the quantity of lead emitted from the metallurgical industry has decreased somewhat because of the application of control equipment and the closing of several plants, particularly in the zinc and pyrometallurgical industries.

A new locus for lead emissions emerged in the mid-1960s with the opening of the "Viburnum Trend" or "New Lead Belt" in southeastern Missouri. The presence of ten mines and three accompanying lead smelters in this area makes it the largest lead-producing district in the world and has moved the United States into first place among the world's lead-producing nations.

Although some contamination of soil and water occurs as a result of such mechanisms as leaching from mine and smelter wastes, quantitative estimates of the extent of this contamination are not available. Spillage of ore concentrates from open trucks and railroad cars, however, is known to contribute significantly to contamination along transportation routes. For example, along two routes used by ore trucks in southeastern Missouri, lead levels in leaf litter ranged from 2000 to 5000 $\mu g/g$ at the roadway, declining to a fairly constant 100 to 200 $\mu g/g$ beyond about 400 ft from the roadway (Wixson et al., 1977).

Another possible source of land or water contamination is the disposal of particulate lead collected by air pollution control systems. The potential impact on soil and water systems from the disposal of dusts collected by these control systems has not been quantified.

5.4 SUMMARY

There is no doubt that atmospheric lead has been a component of the human environment since the earliest written record of civilization. Atmospheric emissions are recorded in glacial ice strata and pond and lake sediments. The history of these global emissions seems closely tied to production of lead by industrially oriented civilizations.

Although the amount of lead emitted from natural sources is a subject of controversy, even the most liberal estimate (25 X 10^3 t/year) is dwarfed by the global emissions from anthropogenic sources (450 X 10^3 t/year).

Production of lead in the United States has remained steady at about 1.2 X 10^6 t/year for the past decade. The gasoline additive share of this market has dropped from 18 to 9.5 percent during the period 1971 to 1981. The contribution of gasoline lead to total atmospheric emissions has remained high, at 85 percent, as emissions from stationary sources have decreased at the same pace as from mobile sources. The decrease in stationary source emissions is due primarily to control of stack emissions, whereas the decrease in mobile source emissions is a result of switchover to unleaded gasolines. The decreasing use of lead in gasoline is projected to continue through 1990.

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6. TRANSPORT AND TRANSFORMATION

6.1 INTRODUCTION

This chapter describes the transition from the emission of lead particles into the atmosphere to their ultimate deposition on environmental surfaces, i.e., vegetation, soil, or water. At the source, lead emissions are typically around 10,000 $\mu g/m^3$ (see Section 5.3.3), while in city air, lead values are usually between 0.1 and 10 $\mu g/m^3$ (Dzubay et al., 1979; Reiter et al., 1977; also see Chapter 7). These reduced concentrations are the result of dilution of effluent gas with clean air and the removal of particles by wet or dry deposition. Characteristically, lead concentrations are highest in confined areas close to sources and are progressively reduced by dilution or deposition in districts more removed from sources.

At any particular location and time, the concentration of lead found in the atmosphere depends on the proximity to the source, the amount of lead emitted from sources, and the degree of mixing provided by the motion of the atmosphere. It is possible to describe quantitatively the physics of atmospheric mixing in a variety of ways and, with some limiting assumptions, to develop simulation models that predict atmospheric lead concentrations. These models are not sensitive to short-term variations in air motion over a period of weeks or months because these variations are suppressed by integration over long periods of time.

In highly confined areas such as parking garages or tunnels, atmospheric lead concentrations can be ten to a thousand times greater than values measured near roadways or in urban areas. In turn, atmospheric lead concentrations are usually about 2½ times greater in the central city than in residential suburbs. Rural areas have even lower concentrations.

Because lead emissions in the United States have declined dramatically in the past few years, the older lead concentration data on which recent dispersion studies are based may seem not to be pertinent to existing conditions. Such studies do in fact illustrate principles of atmospheric dispersion and may validly be applied to existing concentrations of lead, which are described in Section 7.2.1.1.

Transformations which may occur during dispersion are physical changes in particle size distribution, chemical changes from the organic to the inorganic phase, and chemical changes in the inorganic phase of lead particles. Particle size distribution stabilizes within a few hundred kilometers of the sources, although atmospheric concentration continues to decrease with distance. Concentrations of organolead compounds are relatively small (1 to 6 percent of total lead) except in special situations where gasoline is handled or where engines are started cold within confined areas. Ambient organolead concentrations decrease more rapidly than inorganic lead, suggesting conversion from the organic to the inorganic phase during transport. Inorganic lead appears to convert from lead halides and oxides to lead sulfates.

Lead is removed from the atmosphere by wet or dry deposition. The mechanisms of dry deposition have been incorporated into models that estimate the flux of atmospheric lead to the Earth's surface. Of particular interest is deposition on vegetation surfaces, since this lead may be incorporated into food chains. Between wet and dry deposition, it is possible to calculate an atmospheric lead budget that balances the emission inputs discussed in Section 5.3.3. with deposition outputs.

6.2 TRANSPORT OF LEAD IN AIR BY DISPERSION

6.2.1 Fluid Mechanics of Dispersion

Particles in air streams are subject to the same principles of fluid mechanics as particles in flowing water (Friedlander, 1977). On this basis, the authors of several texts have described the mathematical arguments for the mixing of polluted air with clean air (Benarie, 1980; Dobbins, 1979; Pasquill, 1974). The first principle is that of diffusion along a concentration gradient. If the airflow is steady and free of turbulence, the rate of mixing is determined by the diffusivity of the pollutant. In the case of gases, this diffusivity is an inherent property of the molecular forces between gases. For particles, diffusivity is a property of Brownian movement, hence a function of particle size and concentration. For both cases, the diffusivity for dilute media is a constant (Dobbins, 1979).

If the steady flow of air is interrupted by obstacles near the ground, turbulent eddies or vortices may be formed. Diffusivity is no longer constant but may be influenced by factors independent of concentrations, such as windspeed, atmospheric stability, and the nature of the obstacle. By making generalizations of windspeed, stability, and surface roughness, it is possible to construct models using a variable transport factor called eddy diffusivity (K), in which K varies in each direction, including vertically. There is a family of K-theory models that describe the dispersion of particulate pollutants.

The simplest K-theory model assumes that the surface is uniform and the wind is steady; thus, turbulence is predictable for various conditions of atmospheric stability (Pasquill, 1974). This model produces a Gaussian plume, called such because the concentration of the pollutant decreases according to a normal or Gaussian distribution in both the vertical and horizontal directions. These models have some utility and are the basis for most of the air quality simulations performed to date (Benarie, 1980). However, the assumptions of steady windspeed and smooth surface place constraints on their utility.

Several approaches have been used to circumvent the constraints of the Gaussian models. Some have been adapted for studying long range transport (LRT) (more than 100 km) of pollutants. Johnson (1981) discusses 35 LRT models developed during the 1970s to describe the

dispersion of atmospheric sulfur compounds. A few models that address specific problems of local and regional transport merit further discussion because they emphasize the scope of the modeling problem.

One family of models is based on the conservative volume element approach, where volumes of air are seen as discrete parcels having conservative meteorological properties, such as water vapor mixing ratio, potential temperature, and absolute vorticity (Benarie, 1980). The effect of pollutants on these parcels is expressed as a mixing ratio. These parcels of air may be considered to move along a trajectory that follows the advective wind direction. These models are particularly suitable for dealing with surface roughness, but they tend to introduce artifact diffusion or pseudodiffusion, which must be suppressed by calculation (Egan and Mahoney, 1972; Liu and Seinfeld, 1975; Long and Pepper, 1976).

An approach useful for estimating dispersion from a roadway derives from the similarity approach of Prandtl (1927). A mixing length parameter is related to the distance traveled by turbulent eddies during which violent exchange of material occurs. This mixing length is mathematically related to the square root of the shear stress between the atmosphere and the surface. Richardson and Procter (1925) formulated these concepts in a law of atmospheric diffusion which was further extended to boundary layer concepts by Obukhov (1941). At the boundary layer, the turbulent eddy grows and its energy decreases proportionately with time and distance away from the source.

Although physical descriptions of turbulent diffusion exist for idealized circumstances such as isolated roadways and flat terrain, the complex flow and turbulence patterns of cities has defied theoretical description. The permeability of street patterns and turbulent eddy development in street canyons are two major problem areas that make modeling urban atmospheres difficult. Kotake and Sano (1981) have developed a simulation model for describing air flow and pollutant dispersion in various combinations of streets and buildings on two scales. A small scale, 2 to 20 m, is used to define the boundary conditions for 2 to 4 buildings and associated roadways. These subprograms are combined on a large scale of 50 to 500 meters. Simulations for oxides of nitrogen show nonlinear turbulent diffusion, as would be expected. The primary utility of this program is to establish the limits of uncertainty, the first step toward making firm predictions. It is likely that the development of more complete models of dispersion in complex terrains will become a reality in the near future.

An important point in this discussion is that none of the models described above have been tested for lead. The reason for this is simple. All of the models require sampling periods of 2 hours or less in order for the sample to conform to a well-defined set of meteorological conditions. In most cases, such a sample would be below the detection limits

for lead. The common pollutant used to test models is SO_2, which can be measured over very short, nearly instantaneous, time periods. The question of whether gaseous SO_2 can be used as a surrogate for particulate lead in these models remains to be answered.

6.2.2 Influence of Dispersion on Ambient Lead Concentrations

Dispersion within confined situations, such as parking garages, residential garages and tunnels, and away from expressways and other roadways not influenced by complex terrain features depends on emission rates and the volume of clean air available for mixing. These factors are relatively easy to estimate and some effort has been made to describe ambient lead concentrations which can result under selected conditions. On an urban scale, the routes of transport are not clearly defined, but can be inferred from an isopleth, i.e., a plot connecting points of identical ambient concentrations. These plots always show that lead concentrations are maximum where traffic density is highest.

Dispersion beyond cities to regional and remote locations is complicated by the fact that there are no monitoring network data from which to construct isopleths, that removal by deposition plays a more important role with time and distance, and that emissions from many different geographic location's sources converge. Some techniques of source reconciliation are described, but these become less precise with increasing distance from major sources of lead. Dispersion from point sources such as smelters and refineries is described with isopleths in the manner of urban dispersion, although the available data are notably less abundant.

6.2.2.1 Confined and Roadway Situations. Obviously, the more source emissions are diluted by clean air, the lower ambient air concentrations of lead will be. Ingalls and Garbe (1982) used a variety of box and Gaussian plume models to calculate typical levels of automotive air pollutants that might be present in microscale (within 100 meters of the source) situations with limited ventilation. Table 6-1 shows a comparison of six exposure situations, recomputed for a flat-average lead emission factor of 6.3 mg/km for roadway situations and 1.0 mg/min for garage situations. The roadway emission factor chosen corresponds roughly to values chosen by Dzubay et al. (1979) and Pierson and Brachaczek (1976) scaled to 1979 lead-use statistics. The parking garage factor was estimated from roadway factors by correction for fuel consumption (Ingalls and Garbe, 1982).

Confined situations, with low air volumes and little ventilation, allow automotive pollutant concentrations to reach one to three orders of magnitude higher than are found in open air. Thus, parking garages and tunnels are likely to have considerably higher ambient lead concentrations than are found in expressways with high traffic density or in city streets. Purdue et al. (1973) found total lead levels of 1.4 to 2.3 $\mu g/m^3$ in five of six U.S. cities in 1972. In similar samples from an underground parking garage, total lead was 11 to 12 $\mu g/m^3$.

Table 6-1 also shows that the high concentration of automotive lead near roadways declines significantly at distances greater than 100 meters. Dzubay et al. (1979) found lead concentrations of 4 to 20 $\mu g/m^3$ in air over Los Angeles freeways in 1976; at nearby sites off the freeways, concentrations of 0.3 to 4.7 $\mu g/m^3$ were measured.

TABLE 6-1. SUMMARY OF MICROSCALE CONCENTRATIONS

Data are recalculated from Ingalls and Garbe (1982) using 1979 lead emission factors. They show that air lead concentrations in a garage or tunnel can be two or three orders of magnitude higher than on streets or expressways. Typical conditions refer to neutral atmospheric stability and average daily traffic volumes. Severe conditions refer to maximum hourly traffic volume with atmospheric inversion. Data are in $\mu g/m^3$. Emission rates are given in parentheses.

Situation	Air lead concentration	
Residential garage (1 mg Pb/min)		
Typical (30 second idle time)	80	
Severe (5 min idle time)	670	
Parking garage (1 mg Pb/min)		
Typical	40	
Severe	560	
Roadway tunnel (6.3 mg Pb/km)		
Typical	11	
Severe	29	
Street canyon (sidewalk receptor) (6.3 mg Pb/km)		
Typical a) 800 vehicles/hr	0.4	
b) 1,600 vehicles/hr	0.9	
Severe a) 800 vehicles/hr	1.4	
b) 1,600 vehicles/hr	2.8	
On expressway (wind: 315 deg. rel., 1 m/sec) (6.3 mg Pb/km)		
Typical	2.4	
Severe	10	
Beside expressway (6.3 mg Pb/km)	30 min	Annual average
Severe 1 meter	8	1.2
10 meters	6	1.0
100 meters	2	0.3
1,000 meters	0.25	0.03

Tiao and Hillmer (1978) and Ledolter and Tiao (1979) have analyzed 3 years (1974-1977) of ambient air lead data from one site on the San Diego Freeway in Los Angeles, California. Particulate lead concentrations were measured at five locations: in the median strip and at distances of 8 and 30 to 35 meters from the road edge on both sides of the road. Average lead concentrations at the 35 meter point were two- to four-fold lower than at the 8 meter location (Tiao and Hillmer, 1978). An empirical model involving traffic count and traffic speed, which are related to road emissions, required only windspeed as a predictor of dispersion conditions.

Witz et al. (1982) found that meteorological parameters in addition to windspeed, such as inversion frequency, inversion duration, and temperature, correlate well with ambient levels of lead. At a different site near the San Diego freeway in Los Angeles, monthly ambient particulate lead concentrations and meteorological variables were measured about 100 meters from the roadway through 1980. Multiple linear regression analysis showed that temperature at 6 AM, windspeed, wind direction, and a surface-based inversion factor were important variables in accurately predicting monthly average lead concentrations. In this data set, lead values for December were about five-fold higher than those measured in the May to September summer season, suggesting that seasonal variations in wind direction and the occurrence of surface-based inversions favor high winter lead values. Unusually high early morning temperatures and windspeed during the winter increased dispersion and reduced lead concentration. The success of this empirical model depends on the interplay of windspeed and atmospheric stability (Witz et al., 1982).

6.2.2.2 Dispersion of Lead on an Urban Scale. In cities, air pollutants including lead that are emitted from automobiles tend to be highest in concentration in high traffic areas. Most U.S. cities have a well-defined central business district (CBD) where lead concentrations are highest. To illustrate the dispersion of lead experienced in cities, two cases are presented below.

Trijonis et al. (1980) reported lead concentrations for seven sites in St. Louis, Missouri; annual averages for 1977 are shown in Figure 6-1. Values around the CBD are typically two to three times greater than those found in the outlying suburbs in St. Louis County to the west of the city. Bradow (1980) presented results from the Regional Air Monitoring System Gaussian plume model (Turner, 1979) for St. Louis for the 1977 calendar year. Figure 6-1 also presents isopleths for lead concentration calculated from that model. The general picture is one of peak concentrations within congested commercial districts which gradually decline in outlying areas. However, concentration gradients are not steep, and the whole urban area has levels of lead above 0.5 $\mu g/m^3$.

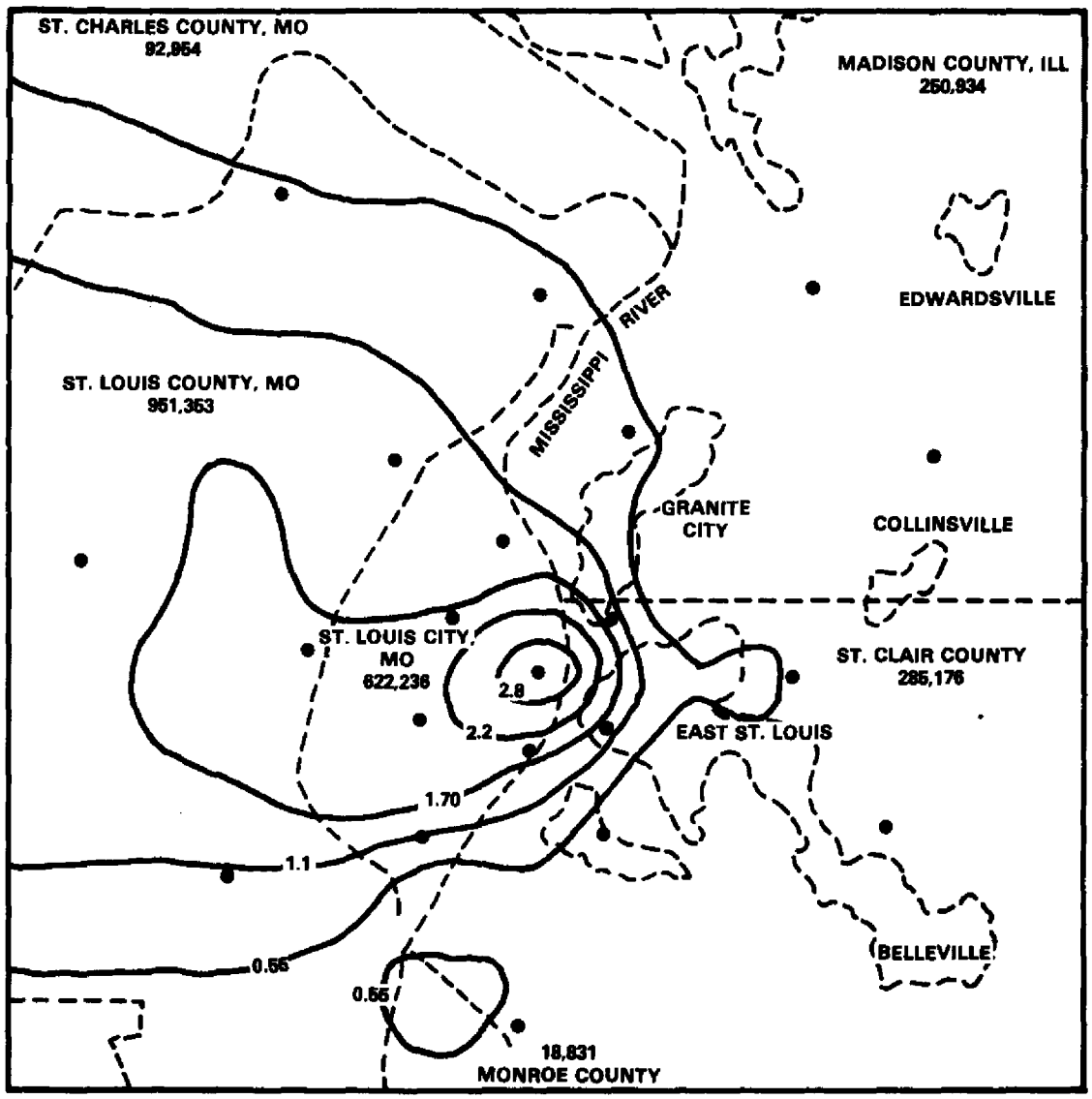

Figure 6-1. Isopleths are shown for annual average particulate lead in $\mu g/m^3$. RAM Model calculations predict lead concentrations in St. Louis for 1977. Numerical values below place names are 1970 population counts for these areas.

Source: Calculated from Bradow (1980) on the basis of a fleet average lead emissions factor of 54 mg/mile for 1977.

For the South Coast Basin of Southern California, the area of high traffic density is more widespread than is characteristic of many cities. Ambient concentrations of lead tend to be more uniform. For example, Figures 6-2 and 6-3 show the average daily traffic by grid square and the contour plots of annual average lead concentration, respectively, for 1969 (Kawecki, 1978). In addition, Figure 6-3 shows annual average lead measured at eight sites in the Basin for that year. It is clear that the central portion had atmospheric particulate lead concentrations in the range of 3 $\mu g/m^3$; the outer areas were about 1 to 2 $\mu g/m^3$.

Reiter et al. (1977) have shown similar results for the town of Fort Collins, Colorado, for a 5.5-hr period in May of 1973. In that study, modeling results showed maximum lead concentrations in the center of town around 0.25 $\mu g/m^3$, which decreased to 0.1 $\mu g/m^3$ in the outermost region. Presumably, still lower values would be found at more remote locations.

Apparently, then, lead in the air decreases 2½-fold from maximum values in center city areas to well populated suburbs, with a further 2-fold decrease in the outlying areas. These modeling estimates are generally confirmed by measurement in the cases cited above and in the data presented in Section 7.2.1.

6.2.2.3 Dispersion from Smelter and Refinery Locations. The 15 mines and 7 primary smelters and refineries shown in Figure 5-3 are not located in urban areas. Most of the 56 secondary smelters and refineries are likewise non-urban. Consequently, dispersion from these point sources should be considered separately, but in a manner similar to the treatment of urban regions. In addition to lead concentrations in air, concentrations in soil and on vegetation surfaces are often used to determine the extent of dispersion away from smelters and refineries.

6.2.2.4 Dispersion to Regional and Remote Locations. Beyond the immediate vicinity of urban areas and smelter sites, lead in air declines rapidly to concentrations of 0.1 to 0.5 $\mu g/m^3$. Two mechanisms responsible for this change are dilution with clean air and removal by deposition (Section 6.4). In the absence of monitoring networks that might identify the sources of lead in remote areas, two techniques of source identification have been used. Vector gradient analysis was attempted by Everett et al. (1979) and source reconciliation has been reported by Sievering et al. (1980) and Cass and McRae (1983). A third technique, isotopic composition, has been used to identify anthropogenic lead in air, sediments, soils, plants, and animals in urban, rural, and remote locations (Chow et al. 1975), but this technique is not discussed here because it provides no information on the mechanism of transport.

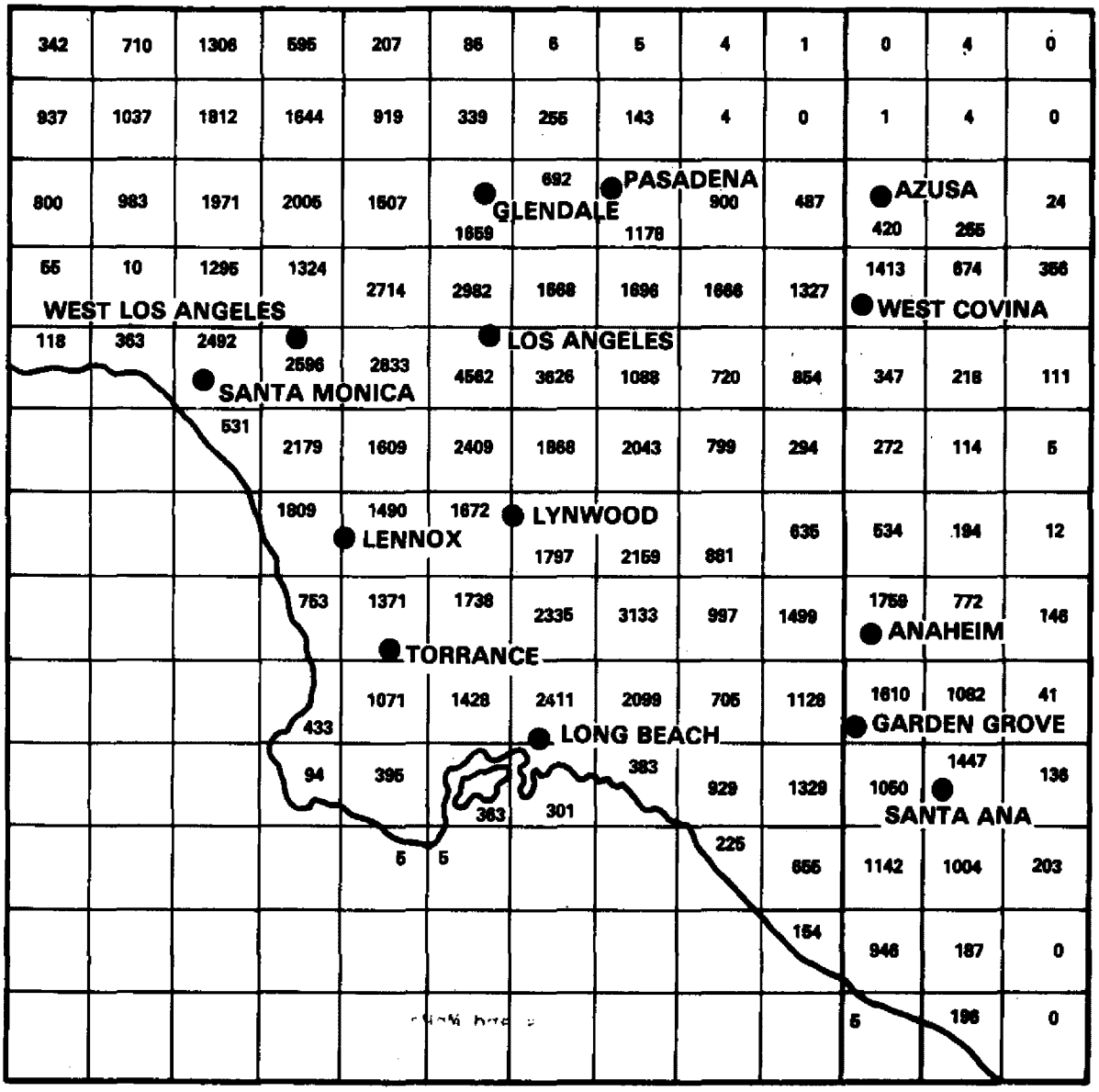

Figure 6-2. Spatial distribution of surface street and freeway traffic in the Los Angeles Basin (10^3 VMT/day) for 1979.

Source: Kawecki (1978).

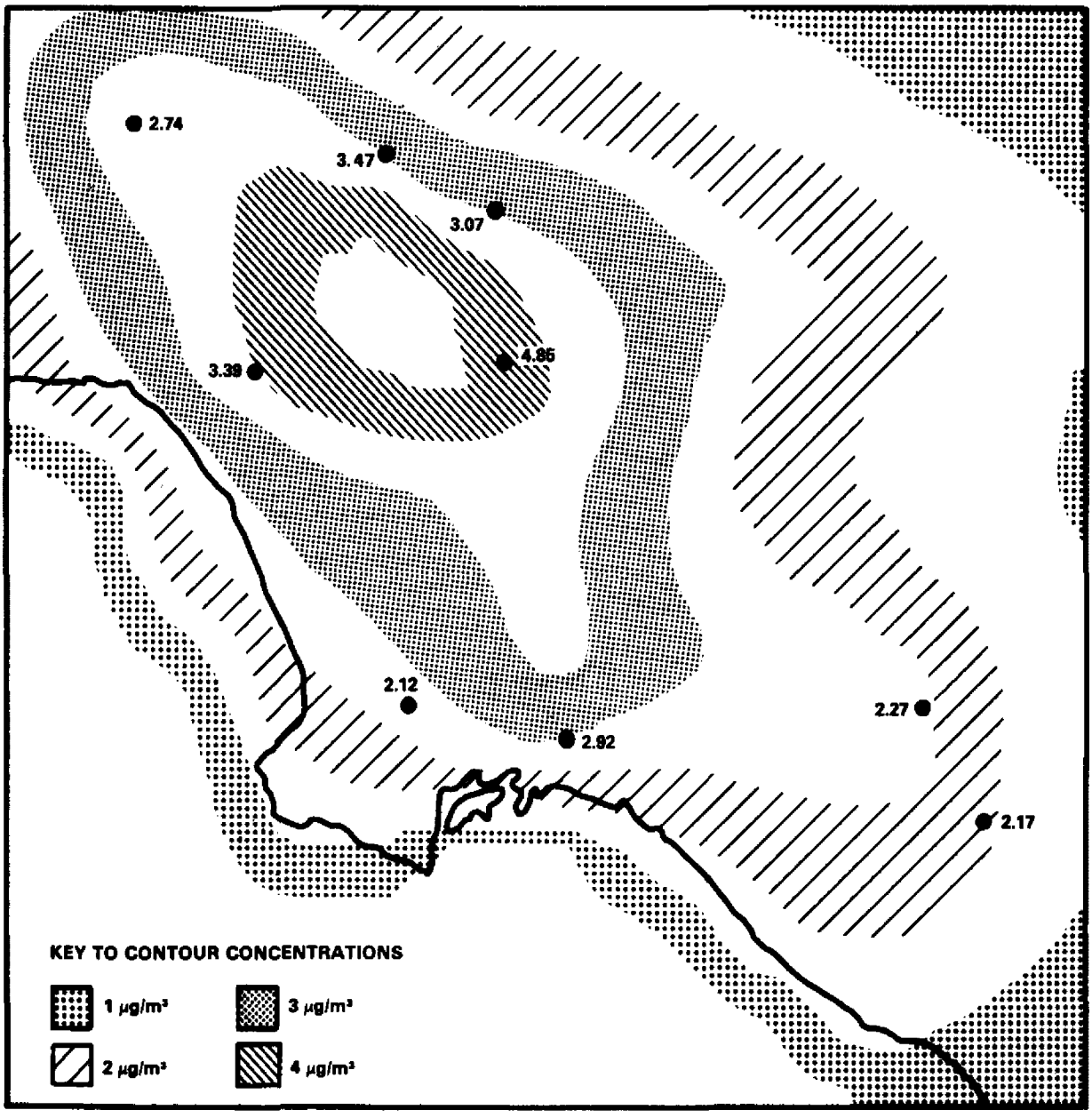

Figure 6-3. Annual average suspended lead concentrations for 1969 in the Los Angeles Basin, calculated from the model of Cass (1975). The white zones between the patterned areas are transitional zones between the indicated concentrations.

Source: Kawecki (1978).

In vector gradient analysis, the sampler is oriented to the direction of the incoming wind vector, and samples are taken only during the time the wind is within a 30° arc of that vector. Other meteorological data are taken continuously. As the wind vector changes, a different sampler is turned on. A 360° plot of concentration vs. wind direction gives the direction from which the pollutant arrives at that location. Only one report of the use of this technique for lead occurs in the literature (Everett et al., 1979), and analysis of this experiment was complicated by the fact that in more than half the samples, the lead concentrations were below the detection limit. The study was conducted at Argonne National Laboratory and the results reflected the influence of automobile traffic east and northeast of this location.

Source reconciliation is based on the concept that each type of natural or anthropogenic emission has a unique combination of elemental concentrations. Measurements of ambient air, properly weighted during multivariate regression analysis, should reflect the relative amount of pollutant derived from each of several sources (Stolzenberg et al., 1982). Sievering et al. (1980) used the method of Stolzenberg et al. (1982) to analyze the transport of urban air from Chicago over Lake Michigan. They found that 95 percent of the lead in Lake Michigan air could be attributed to various anthropogenic sources, namely coal fly ash, cement manufacture, iron and steel manufacture, agricultural soil dust, construction soil dust, and incineration emissions. This information alone does not describe transport processes, but the study was repeated for several locations to show the changing influence of each source.

Cass and McRae (1983) used source reconciliation in the Los Angeles Basin to interpret 1976 NFAN data (see Sections 4.2.1 and 7.2.1.1) based on emission profiles from several sources. They developed a chemical element balance model, a chemical tracer model, and a multivariate statistical model. The chemical element balance model showed that 20 to 22 percent of the total suspended particle mass could be attributed to highway sources. The chemical tracer model permitted the lead concentration alone to represent the highway profile, since lead comprised about 12 percent of the mass of the highway generated aerosol. The multivariate statistical model used only air quality data without source emission profiles to estimate stoichiometric coefficients of the model equation. The study showed that single element concentrations can be used to predict the mass of total suspended particles.

A type of source reconciliation, chemical mass balance, has been used for many years by geochemists in determining the anthropogenic influence on the global distribution of elements. Two studies that have applied this technique to the transport of lead to remote areas are Murozumi et al. (1969) and Shirahata et al. (1980). In these studies, the influence of natural or crustal lead was determined by mass balance, and the relative influence of

anthropogenic lead was determined. In the Shirahata et al. (1980) study, the influence of anthropogenic lead was confirmed quantitatively by analysis of isotopic compositions in the manner of Chow et al. (1975).

Harrison and Williams (1982) determined air concentrations, particle size distributions, and total deposition flux at one urban and two rural sites in England. The urban site, which had no apparent industrial, commercial or municipal emission sources, had an air lead concentration of 3.8 $\mu g/m^3$, whereas the two rural sites were about 0.15 $\mu g/m^3$. The average particle size became smaller toward the rural sites, as the mass median equivalent diameter (MMED) shifted downward from 0.5 μm to 0.1 μm. The total deposition flux will be discussed in Section 6.4.2.

Knowledge of lead concentrations in the oceans and glaciers provides some insight into the degrees of atmospheric mixing and long range transport. Tatsumoto and Patterson (1963), Chow and Patterson (1966), and Schaule and Patterson (1980) measured dissolved lead concentrations in sea water off the coast of California, in the Central North Atlantic (near Bermuda), and in the Mediterranean, respectively. The profile obtained by Schaule and Patterson (1980) is shown in Figure 6-4. Surface concentrations in the Pacific (14 ng/kg) were found to be higher than those of the Mediterranean or the Atlantic, decreasing abruptly with depth to a relatively constant level of 1 to 2 ng/kg. The vertical gradient was found to be much less in the Atlantic. Tatsumoto and Patterson (1963) had earlier estimated an average surface lead concentration of 200 ng/kg in the northern hemispheric oceans. Chow and Patterson (1966) revised this estimate downward to 70 ng/kg. Below the mixing layer, there appears to be no difference between lead concentrations in the Atlantic and Pacific. These investigators calculated that industrial lead currently is being added to the oceans at about 10 times the rate of introduction by natural weathering, with significant amounts being removed from the atmosphere by wet and dry deposition directly into the ocean. Their data suggest considerable contamination of surface waters near shore, diminishing toward the open ocean (Chow and Patterson, 1966).

Duce et al. (1975), Taylor (1964), and Maenhaut et al. (1979) have investigated trace metal concentrations (including lead) in the atmosphere in remote northern and southern hemispheric sites. The natural sources for such atmospheric trace metals include the oceans and the weathering of the Earth's crust, while the anthropogenic source is particulate air pollution. Enrichment factors for concentrations relative to standard values for the oceans and the crust were calculated (Table 6-2); the mean crustal enrichment factors for the North Atlantic and the South Pole are shown in Figures 6-5 and 6-6. The significance of the comparison in Figure 6-6 is that 90 percent of the particulate pollutants in the global

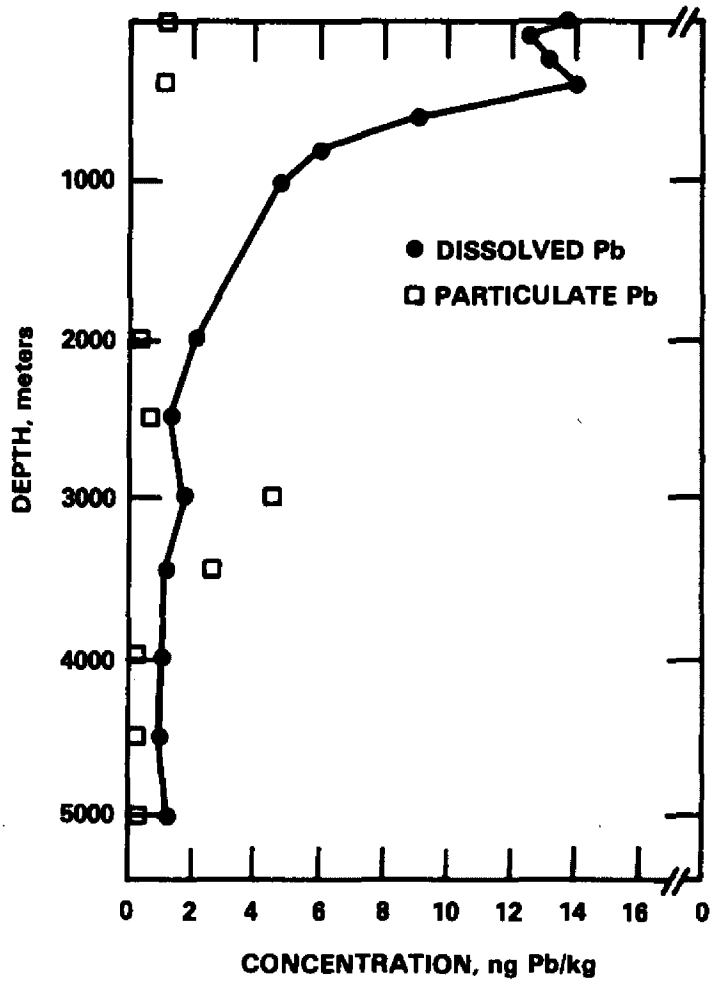

Figure 6-4. Profile of lead concentrations in the central northeast Pacific. Values below 1000 m are an order of magnitude lower than reported by Tatsumoto and Patterson (1963) and Chow and Patterson (1966).

Source: Schaule and Patterson (1980).

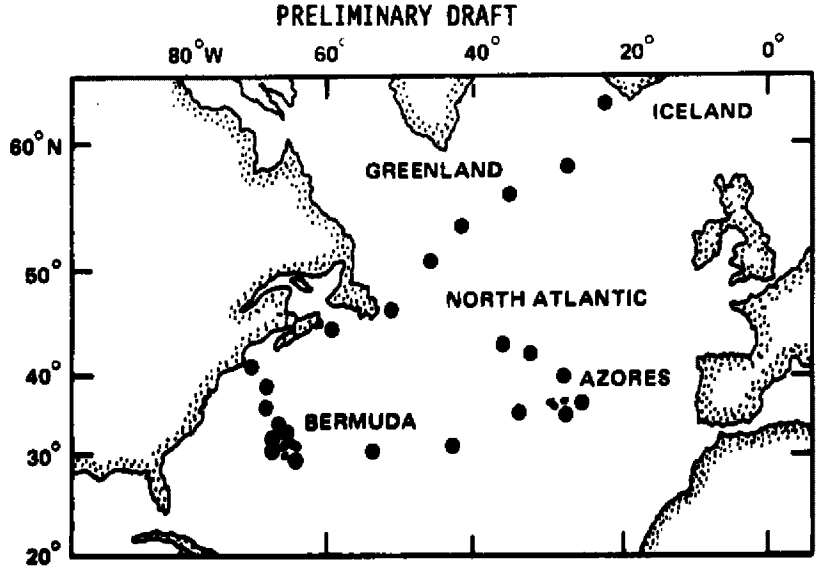

Figure 6-5. Midpoint collection location for atmospheric samples collected from R.V. Trident north of 30 N, 1970—1972.

Source: Duce et al. (1975); Zoller et al. (1974).

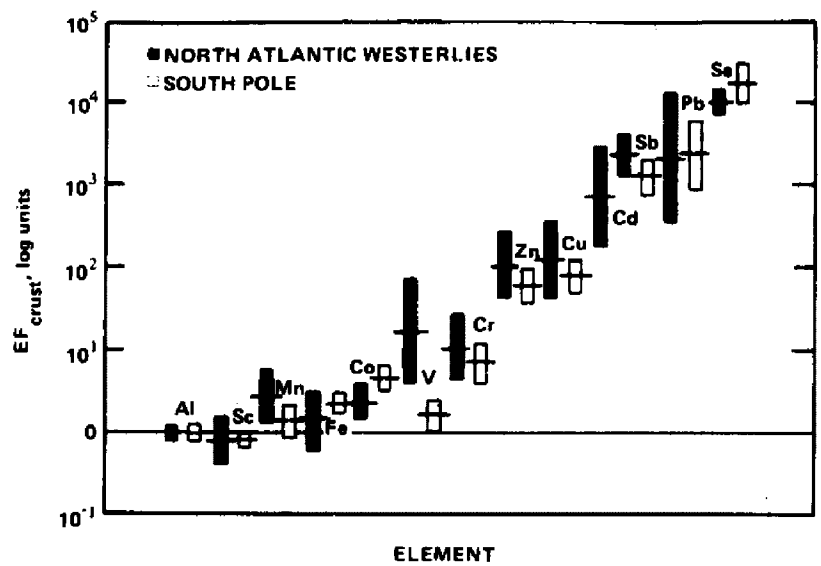

Figure 6-6. The EF_{crust} values for atmospheric trace metals collected in the North Atlantic westerlies and at the South Pole. The horizontal bars represent the geometric mean enrichment factors, and the vertical bars represent the geometric standard deviation of the mean enrichment factors. The EF_{crust} for lead at the South Pole is based on the lowest lead concentration (0.2 mg/scm).

Source: Duce et al. (1975); Zoller et al. (1974).

troposphere are injected in the northern hemisphere (Robinson and Robbins, 1971). Since the residence times for particles in the troposphere (Poet et al., 1972) are much less than the interhemispheric mixing time, it is unlikely that significant amounts of particulate pollutants can migrate from the northern to the southern hemisphere via the troposphere; however, this does not rule out stratospheric transfer.

TABLE 6-2. ENRICHMENT OF ATMOSPHERIC AEROSOLS OVER CRUSTAL ABUNDANCE

Using the crustal abundances of Taylor (1964), the enrichment of atmospheric aerosols, relative to aluminum, has been calculated by Duce et al. (1975). An enrichment factor significantly above one implies a source other than crustal rock for the element in question.

Element	Concentration range, ng/m^3	Enrichment factor[a]
Al	8-370	1.0
Si	0:0008-0.011	0.8
Fe	3.4-220	1.4
Co	0.006-0.09	2.4
Mn	0.05-5.4	2.6
Cr	0.07-1.1	11
V	0.06-14	17
Zn	0.3-27	110
Cu	0.12-10	120
Cd	0.003-0.62	730
Pb	0.10-64	2,200
Sb	0.05-0.64	2,300
Se	0.09-0.40	10,000

[a]Based on the geometric mean of the concentration.

Murozumi et al. (1969) have shown that long range transport of lead particles emitted from automobiles has significantly polluted the polar glaciers. They collected samples of snow and ice from Greenland and the Antarctic. As shown in Figure 6-7, they found that the concentration of lead varied inversely with the geological age of the sample. The authors

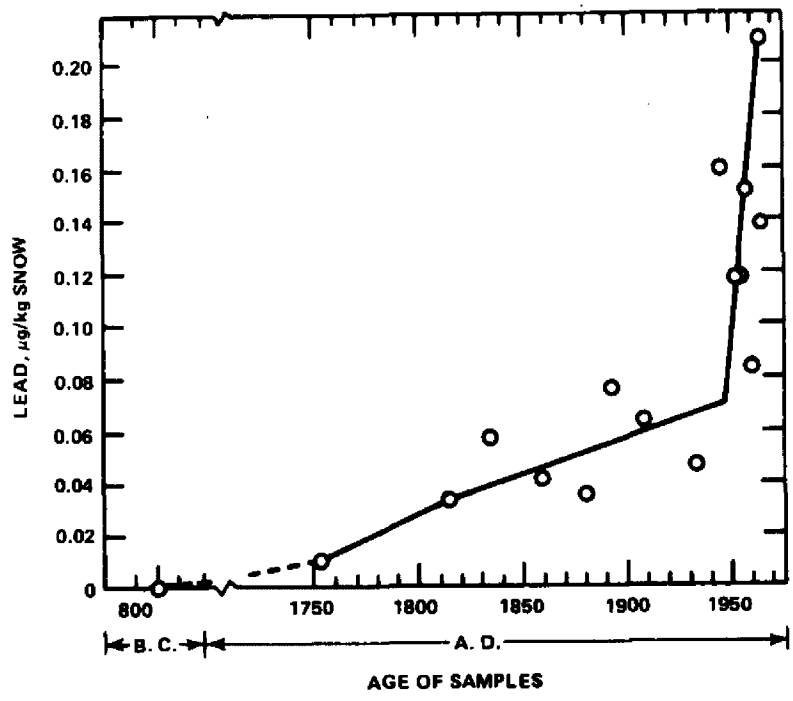

Figure 6-7. Lead concentration profile in snow strata of Northern Greenland.

Source: Murozumi et al. (1969).

attribute the gradient increase after 1750 to the Industrial Revolution and the accelerated increase after 1940 to the increased use of lead alkyls in gasoline. The most recent levels found in the Antarctic snows were, however, less than those found in Greenland by a factor of 10 or more. Before 1940 the concentrations in the Antarctic were below the detectable level (<0.001 µg/kg) and have risen to 0.2 µg/kg in recent snow.

Jaworowski (1967) found that lead concentrations in two glaciers have increased by a factor of 10 during the last century. The concentrations in the most recent ice layers were extremely high (148 µg/kg). Jaworowski et al. (1975) also studied stable and radioactive pollutants from ice samples from the Storbreen glaciers in Norway. The mean stable lead concentration in Storbreen glacier ice in the 12th century was 2.1 µg/kg. The mean for more recent samples was 9.9 µg/kg. Around 1870 the average lead concentration in Norwegian glacier ice was 5.9 µg/kg, whereas that for glaciers in Poland was 5.0 µg/kg. A century later, the mean concentration in the Norwegian glacier was 9.9 µg/kg, while the mean concentration in the Polish glacier reached 148 µg/kg. Jaworowski et al. (1975) attributed the large increase of lead concentrations in the Polish glacier to local sources.

Evidence from remote areas of the world suggests that lead and other fine particle components are transported substantial distances, up to thousands of kilometers, by general weather systems. The degree of surface contamination of remote areas with lead depends both on weather influences and on the degree of air contamination. However, even in remote areas, man's primitive activities can play an important role in atmospheric lead levels. Davidson et al. (1982) have shown that there are significant levels of fine particle lead, up to 0.5 $\mu g/m^3$, in remote villages in Nepal. The apparent source is combustion of dried yak dung, which contains small amounts of naturally occurring lead derived from plant life in those remote valleys.

6.3 TRANSFORMATION OF LEAD IN AIR

6.3.1 Particle Size Distribution

Whitby et al. (1975) placed atmospheric particles into three different size regimes: the nuclei mode (<0.1 μm), the accumulation mode (0.1 to 2 μm) and the large particle mode (>2 μm). At the source, lead particles are generally in the nuclei and large particle modes. Large particles are removed by deposition close to the source and particles in the nuclei mode diffuse to surfaces or agglomerate while airborne to form larger particles of the accumulation mode. Thus it is in the accumulation mode that particles are dispersed great distances.

In Figure 6-8, size distributions for lead particles in automobile exhaust are compared with those found in air samples at a receptor site in Pasadena, California, "not in the immediate influence of traffic" (Huntzicker et al., 1975). The authors conclude that the large particle mode found in exhaust (>9 μm) is severely attenuated in ambient air samples. Therefore, large particle lead must be deposited near roadways. Similar data and conclusions had been reported earlier by Daines et al. (1970).

Pierson and Brachaczek (1976) reported particle size distributions that were larger in ambient air than in a roadway tunnel, where vehicle exhaust must be dominant (see Figure 6-9). The large particles may have been deposited in the roadway itself and small particles may have agglomerated during transport from the roadway to the immediate roadside. Since 40 to 1,000 μm particles are found in gutter debris (Figure 6-10), deposition of large particles appears confirmed.

Little and Wiffen (1977, 1978) reported a MMED for lead of 0.1 μm in the roadway but 0.3 μm 1 meter from the road edge in an intercity expressway in England. Further, particle size distributions reported by Huntzicker et al. (1975) show bimodal distributions for on-roadway samples, with peak mass values at about 0.1 and 10 μm. For off-roadway Pasadena samples, there is no evidence of bimodality and only a broad maximum in lead mass between 0.1 and 1 μm.

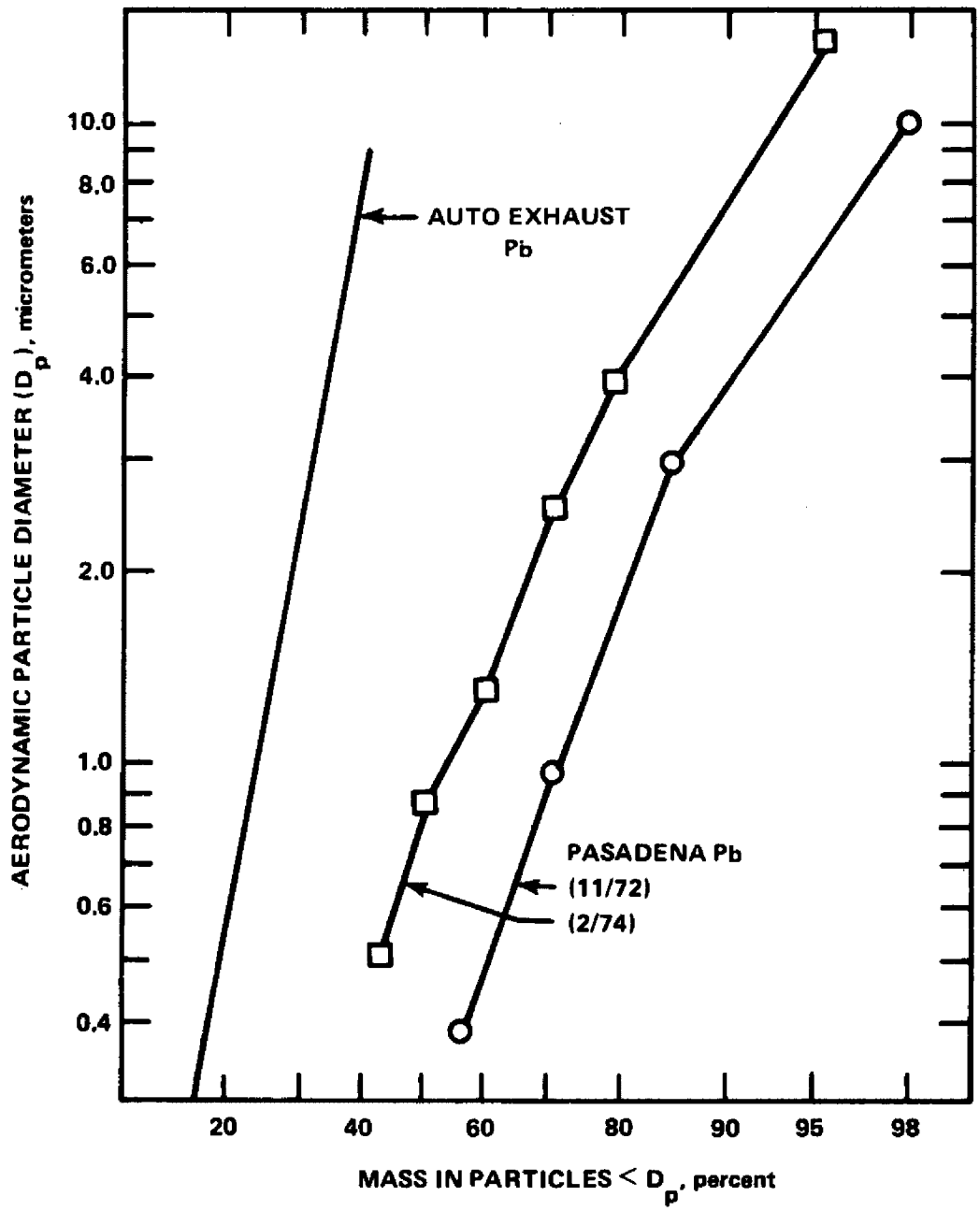

Figure 6-8. Cumulative mass distribution for lead particles in auto exhaust and at an urban site in Pasadena, Calif. some distance from high traffic density roadways.

Source: Huntzicker et al. (1975).

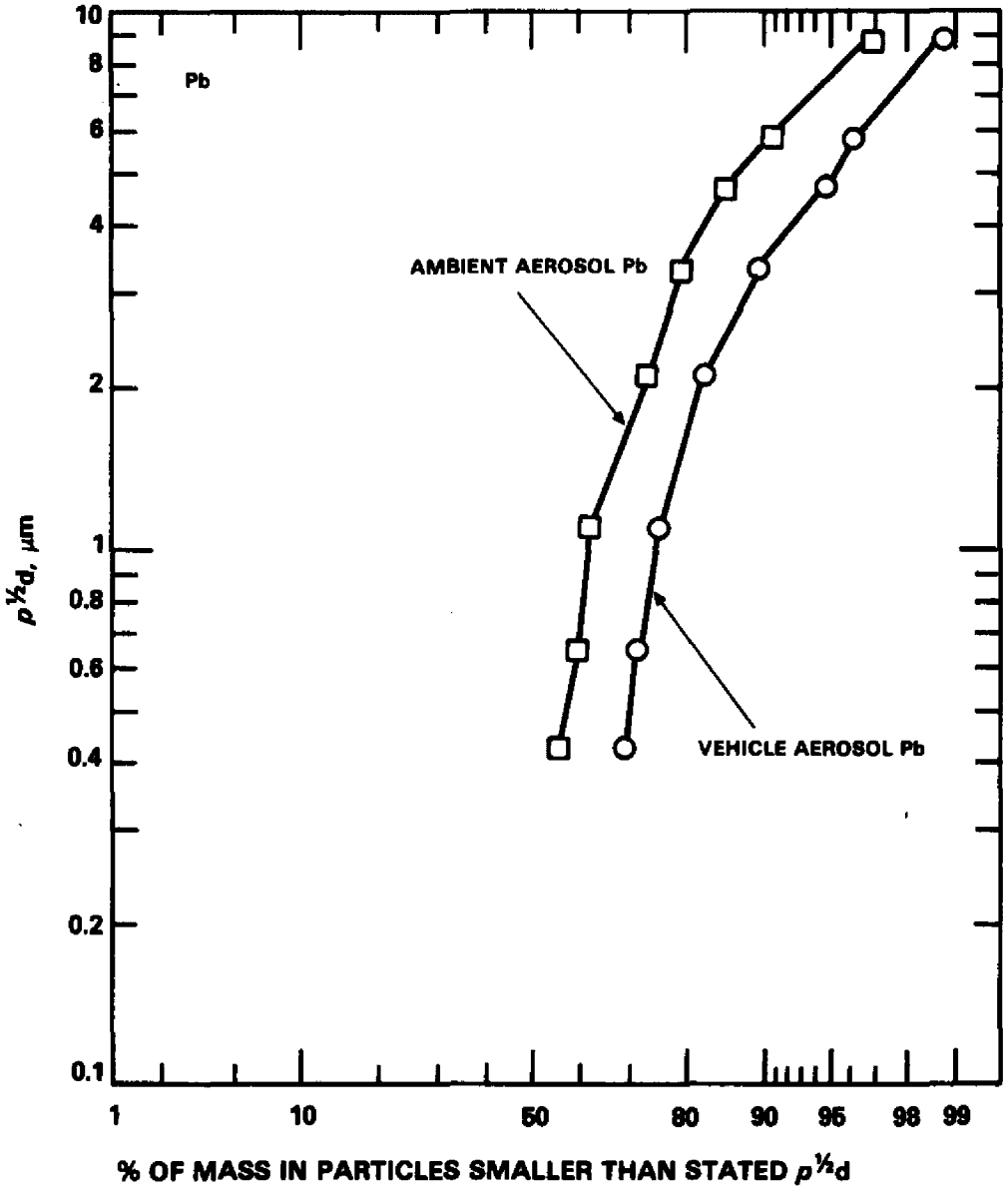

Figure 6-9. Particulate lead size distribution measured at the Allegheny Mountain Tunnel, Pennsylvania Turnpike, 1975.

Source: Pierson and Brachaczek (1976).

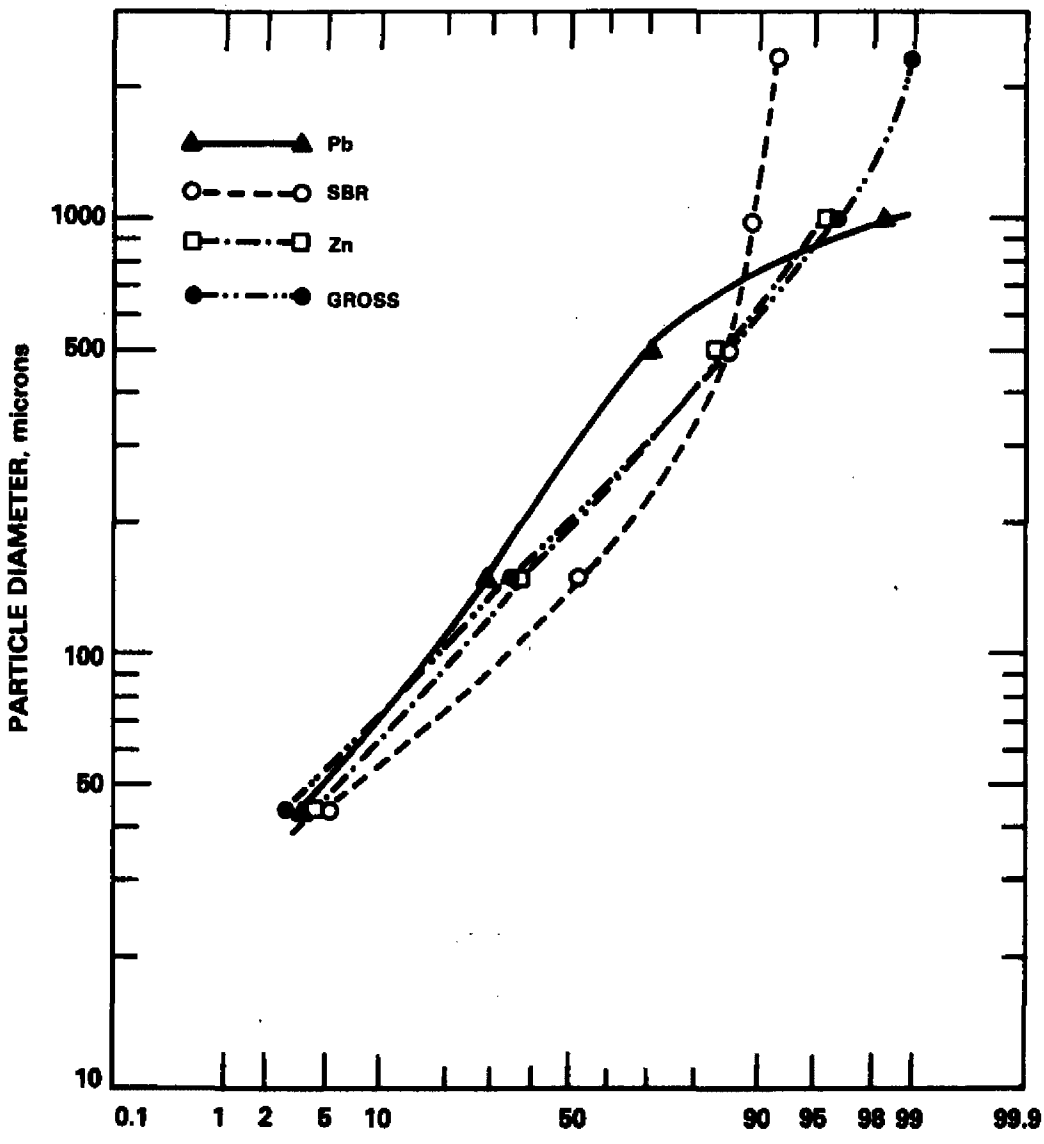

Figure 6-10. Particle size distributions of substances in gutter debris, Rotunda Drive, Dearborn, Michigan.

Source: Pierson and Brachaczek (1976).

In cities or in rural areas, there is a remarkable consistency in lead particle size range. For example, Robinson and Ludwig (1964) report cascade impactor MMED values for lead ranging from 0.23 to 0.3 μm in six U.S. cities and three rural areas as shown in Table 6-3. Stevens et al. (1978) have reported dichotomous sampler data for six U.S. cities, as shown in Table 6-4, and Stevens et al. (1980, 1982) have reported similar results for remote locations. Virtually every other study reported in the literature for Europe, South America, and Asia has come to the conclusion that ambient urban and rural air contains predominantly fine particles (Cholak et al., 1968; De Jonghe and Adams, 1980; Durando and Aragon, 1982; Lee et al., 1968; Htun and Ramachandran, 1977).

TABLE 6-3. COMPARISON OF SIZE DISTRIBUTIONS OF LEAD-CONTAINING PARTICLES IN MAJOR SAMPLING AREAS

		Distribution by particle size, μm					
		25%[a]		MMED		75%[a]	
Sample area	No. of samples	Avg.	Range	Avg.	Range	Avg.	Range
Chicago	12	0.19(7)[b]	0.10-0.29	0.30	0.16-0.64	0.40(10)	0.28-0.63
Cincinnati	7	0.15(3)	0.09-0.24	0.23	0.16-0.28	0.44	0.30-0.68
Philadelphia	7	0.14(3)	0.09-0.25	0.24	0.19-0.31	0.41	0.28-0.56
Los Angeles	8	0.16(7)	0.10-0.22	0.26	0.19-0.29	0.49(7)	0.39-0.60
Pasadena	7	0.18	0.05-0.25	0.24	0.08-0.32	0.48(6)	0.13-0.67
San Francisco	3	0.11	0.06-0.13	0.25	0.15-0.31	0.45(2)	0.44-0.46
Vernon (rural)	5	0.17(4)	0.12-0.22	0.24	0.18-0.32	0.40	0.28-0.47
Cherokee (rural)	1	0.25		0.31		0.71	
Mojave (rural)	1	-		0.27		0.34	

[a]% refers to the percentile of the mass distribution. Thus in the column labeled 25% are the particle sizes at which 25% of the particle mass is in smaller sizes. Similarly, the 75% column contains values of particle sizes at which 75% of the mass is in smaller sizes.
[b]Numbers in parentheses indicate number of samples available for a specific value when different from total number of samples.

Source: Robinson and Ludwig (1964).

TABLE 6-4. DISTRIBUTION OF LEAD IN TWO SIZE FRACTIONS AT SEVERAL SITES IN THE UNITED STATES ($\mu g/m^3$)

Location	Date	Fine	Coarse	F/C ratio
New York, NY	2/1977	1.1	0.18	6.0
Philadelphia, PA	2-3/1977	0.95	0.17	5.6
Charlestown, W. WA	4-8/1976	0.62	0.13	4.6
St. Louis, MO	12/1975	0.83	0.24	3.4
Portland, OR	12/1977	0.87	0.17	5.0
Glendora, CA	3/1977	0.61	0.09	6.7
Average				5.2

Source: Stevens et al. (1978).

It appears that lead particle size distributions are stabilized close to roadways and remain constant with transport into remote environments (Gillette and Winchester, 1972).

6.3.2 Organic (Vapor Phase) Lead in Air

Although lead additives used in gasoline are less volatile than gasoline itself (see Section 3.4), small amounts may escape to the atmosphere by evaporation from fuel systems or storage facilities. Tetraethyllead (TEL) and tetramethyllead (TML) photochemically decompose when they reach the atmosphere (Huntzicker et al., 1975; National Air Pollution Control Administration, 1965). The lifetime of TML is longer than that of TEL. Laveskog (1971) found that transient peak concentrations of organolead up to 5,000 $\mu g/m^3$ in exhaust gas may be reached in a cold-started, fully choked, and poorly tuned vehicle. If a vehicle with such emissions were to pass a sampling station on a street where the lead level might typically be 0.02 to 0.04 $\mu g/m^3$, a peak of about 0.5 $\mu g/m^3$ could be measured as the car passed by. The data reported by Laveskog were obtained with a procedure that collected very small (100 ml), short-time (10 min) air samples. Harrison et al. (1975) found levels as high as 0.59 $\mu g/m^3$ (9.7 percent of total lead) at a busy gasoline service station in England. Grandjean and Nielsen (1977), using GC-MS techniques, found elevated levels (0.1 $\mu g/m^3$) of TML in city streets in Denmark and Norway. These authors attributed these results to the volatility of TML compared with TEL.

A number of studies have used gas absorbers behind filters to trap vapor-phase lead compounds. Because it is not clear that all the lead captured in the backup traps is, in fact, in the vapor phase in the atmosphere, "organic" or "vapor phase" lead is an operational definition in these studies. Purdue et al. (1973) measured both particulate and organic lead in atmospheric samples. They found that the vapor phase lead was about 5 percent of the total lead in most samples. The results are consistent with the studies of Huntzicker et al. (1975) who reported an organic component of 6 percent of the total airborne lead in Pasadena for a 3-day period in June, 1974, and of Skogerboe (1975), who measured fractions in the range of 4 to 12 percent at a site in Fort Collins, Colorado. It is noteworthy, however, that in an underground garage, total lead concentrations were approximately five times those in ambient urban atmospheres, and the organic lead increased to approximately 17 percent.

Harrison et al. (1979) report typical organolead percentages in ambient urban air of 1 to 6 percent. Rohbock et al. (1980) reported higher fractions, up to 20 percent, but the data and interpretations have been questioned by Harrison and Laxen (1980). Rohbock et al. (1980) and De Jonghe and Adams (1980) report one to two orders of magnitude decrease in organolead concentrations from the central urban areas to residential areas.

6.3.3 Chemical Transformations of Inorganic Lead in Air

Lead is emitted into the air from automobiles as lead halides and as double salts with ammonium halides (e.g., $PbBrCl \cdot 2NH_4Cl$). From mines and smelters, $PbSO_4$, $PbO \cdot PbSO_4$, and PbS appear to be the dominant species. In the atmosphere, lead is present mainly as the sulfate with minor amounts of halides. It is not completely clear just how the chemical composition changes in transport.

Biggins and Harrison (1978, 1979) have studied the chemical composition of lead particles in exhaust and in city air in England by X-ray diffractometry. These authors reported that the dominant exhaust forms were PbBrCl, $PbBrCl \cdot 2NH_4Cl$, and α-$2PbBrCl \cdot NH_4Cl$, in agreement with the earlier studies of Hirschler and Gilbert (1964) and Ter Haar and Bayard (1971).

At sampling sites in Lancaster, England, Biggins and Harrison (1978, 1979) found $PbSO_4 \cdot (NH_4)_2SO_4$, and $PbSO_4 \cdot (NH_4)_2BrCl$ together with minor amounts of the lead halides and double salts found in auto exhaust. These authors suggested that emitted lead halides react with acidic gases or aerosol components (SO_2 or H_2SO_4) on filters to form substantial levels of sulfate salts. It is not clear whether reactions with SO_4 occurs in the atmosphere or on the sample filter.

The ratio of Br to Pb is often cited as an indication of automotive emissions. From the mixtures commonly used in gasoline additives, the mass Br/Pb ratio should be about 0.386 if there has been no fractionation of either element (Harrison and Sturges, 1983). However, several authors have reported loss of halide, preferentially bromine, from lead salts in atmospheric transport (Dzubay and Stevens, 1973; Pierrard, 1969; Ter Haar and Bayard, 1971). Both photochemical decomposition (Lee et al., 1971; Ter Haar and Bayard, 1971) and acidic gas displacement (Robbins and Snitz, 1972) have been postulated as mechanisms. Chang et al. (1977) have reported only very slow decomposition of lead bromochloride in natural sunlight; currently the acid displacement of halide seems to be the most likely mechanism. O'Connor et al. (1977) have reported no loss in bromine in comparison of roadside and suburban-rural aerosol samples from western Australia; low levels of SO_2 and sulfate aerosol could account for that result. Harrison and Sturges (1983) warn of several other factors that can alter the Br/Pb ratio. Bromine may pass through the filter as hydrogen bromide gas, lead may be retained in the exhaust system, or bromine may be added to the atmosphere from other sources, such as marine aerosols. They concluded that Br/Pb ratios are only crude estimates of automobile emissions, and that this ratio would decrease with distance from the highway from 0.39 to 0.35 less proximate sites and 0.25 in suburban residential areas.

Habibi et al. (1970) studied the composition of auto exhaust particles as a function of particle size. Their main conclusions follow:

1. Chemical composition of emitted exhaust particles is related to particle size.

    a. Very large particles greater than 200 μm have a composition similar to lead-containing material deposited in the exhaust system, confirming that they have been emitted from the exhaust system. These particles contain approximately 60 to 65 percent lead salts, 30 to 35 percent ferric oxide (Fe_2O_3), and 2 to 3 percent soot and carbonaceous material. The major lead salt is lead bromochloride (PbBrCl), with (15 to 17 percent) lead oxide (PbO) occurring as the $2PbO \cdot PbBrCl$ double salt. Lead sulfate and lead phosphate account for 5 to 6 percent of these deposits. (These compositions resulted from the combustion of low-sulfur and low-phosphorus fuel.)

    b. PbBrCl is the major lead salt in particles of 2 to 10 μm equivalent diameter, with $2PbBrCl \cdot NH_4Cl$ present as a minor constituent.

    c. Submicrometer-sized lead salts are primarily $2PbBrCl \cdot NH_4Cl$.

2. Lead-halogen molar ratios in particles of less than 10 μm MMED indicate that much more halogen is associated with these solids than the amount expected from the presence of $2PbBrCl \cdot NH_4Cl$, as identified by X-ray diffraction. This is particularly true for particles in the 0.5 to 2 μm size range.

3. There is considerably more soot and carbonaceous material associated with fine-mode particles than with coarse mode particles re-entrained after having been deposited after emission from the exhaust system. This carbonaceous material accounts for 15 to 20 percent of the fine particles.

4. Particulate matter emitted under typical driving conditions is rich in carbonaceous material. There is substantially less such material emitted under continuous hot operation.

5. Only small quantities of $2PbBrCl \cdot NH_4Cl$ were found in samples collected at the tailpipe from the hot exhaust gas. Its formation therefore takes place primarily during cooling and mixing of exhaust with ambient air.

Foster and Lott (1980) used X-ray diffractometry to study the composition of lead compounds associated with ore handling, sintering, and blast furnace operations around a lead smelter in Missouri. Lead sulfide was the main constituent of those samples associated with ore handling and fugitive dust from open mounds of ore concentrate. The major constituents from sintering and blast furnace operations appeared to be $PbSO_4$ and $PbO \cdot PbSO_4$, respectively.

6.4 REMOVAL OF LEAD FROM THE ATMOSPHERE

Before atmospheric lead can have any effect on organisms or ecosystems, it must be transferred from the air to a surface. For natural ground surfaces and vegetation, this process may be either dry or wet deposition.

6.4.1 Dry Deposition

6.4.1.1 Mechanisms of Dry Deposition. Transfer by dry deposition requires that the particle move from the main airstream through the boundary layer to a surface. The boundary layer is defined as the region of minimal air flow immediately adjacent to that surface. The thickness of the boundary layer depends mostly on the windspeed and roughness of the surface.

Airborne particles do not follow a smooth, straight path in the airstream. On the contrary, the path of a particle may be affected by micro-turbulent air currents, gravitation, or its own inertia. There are several mechanisms which alter the particle path sufficient to cause transfer to a surface. These mechanisms are a function of particle size, windspeed, and surface characteristics.

Particles larger than a few micrometers in diameter are influenced primarily by sedimentation, where the particle accelerates downward until aerodynamic drag is exactly balanced by gravitational force. The particle continues at this velocity until it reaches a surface. Sedimentation is not influenced by windspeed or surface characteristics. Particles moving in an airstream may be removed by impaction whenever they are unable to follow the airstream around roughness elements of the surface, such as leaves, branches, or tree trunks. In this case, the particle moves parallel to the airstream and strikes a surface perpendicular to the airstream. A related mechanism, turbulent inertial deposition, occurs when a particle encounters turbulence within the airstream causing the particle to move perpendicular to the airstream. It may then strike a surface parallel to the airstream. In two mechanisms, wind eddy diffusion and interception, the particle remains in the airstream until it is transferred to a surface. With wind eddy diffusion, the particle is transported downward by turbulent eddies. Interception occurs when the particle in the airstream passes within one particle radius of a surface. This mechanism is more a function of particle size than windspeed. The final mechanism, Brownian diffusion, is important for very small particles at very low windspeeds. Brownian diffusion is motion, caused by random collision with molecules, in the direction of a decreasing concentration gradient.

Transfer from the main airstream to the boundary layer is usually by sedimentation or wind eddy diffusion. From the boundary layer to the surface, transfer may be by any of the six mechanisms, although those which are independent of windspeed (sedimentation, interception, Brownian diffusion) are more likely.

6.4.1.2 Dry deposition models. A particle influenced only by sedimentation may be considered to be moving downward at a specific velocity usually expressed in cm/sec. Similarly, particles transported to a surface by any mechanism are said to have an effective deposition velocity (V_d), which is measured not by rate of particle movement but by accumulation on a surface as a function of air concentration. This relationship is expressed in the equation:

$$V_d = J/C$$

where J is the flux or accumulation expressed in $ng/cm^2 \cdot s$ and C is the air concentration in ng/cm^3. The units of V_d become cm/sec.

Several recent models of dry deposition have evolved from the theoretical discussion of Fuchs (1964) and the wind tunnel experiments of Chamberlain (1966). From those early works, it was obvious that the transfer of particles from the atmosphere to the Earth's surface involved more than rain or snow. The models of Slinn (1982) and Davidson et al. (1982) are particularly useful for lead deposition and were strongly influenced by the theoretical

discussions of fluid dynamics by Friedlander (1977). Slinn's model considers a multitude of vegetation parameters to find several approximate solutions for particles in the size range of 0.1 to 1.0 μm. In the absence of appropriate field studies, Slinn (1982) estimates deposition velocities of 0.01 to 0.1 cm/sec.

The model of Davidson et al. (1982) is based on detailed vegetation measurements and wind data to predict a V_d of 0.05 to 1.0 cm/sec. Deposition velocities are specific for each vegetation type. This approach has the advantage of using vegetation parameters of the type made for vegetation analysis in ecological studies (density, leaf area index (LAI), height, diameter) and thus may be applicable to a broad range of vegetation types for which data are already available in the ecological literature.

Both models show a decrease in deposition velocity with decreasing particle size down to about 0.1 to 0.2 μm, followed by an increase in V_d with decreasing diameter from 0.1 to 0.001 cm/sec. On a log plot of diameter vs. V_d, this curve is v-shaped, and the plots of several vegetation types show large changes (10X) in minimum V_d, although the minima commonly occur at about the same particle diameter (Figure 6-11).

In summary, it is not correct to assume that air concentration and particle size alone determine the flux of lead from the atmosphere to terrestrial surfaces. The type of vegetation canopy and the influence of the canopy on windspeed are important predictors of dry deposition. Both of these models predict deposition velocities more than one order of magnitude lower than reported in several earlier studies (e.g., Sehmel and Hodgson, 1976).

6.4.1.3 Calculation of Dry Deposition. The data required for calculating the flux of lead from the atmosphere by dry deposition are leaf area index, windspeed, deposition velocity, and air concentration by particle size. The LAI should be total surface rather than upfacing surface, as used in photosynthetic productivity measurements. Leaf area indices should also be expressed for the entire community rather than by individual plant, in order to incorporate variations in density. Some models use a more generalized surface roughness parameter, in which case the deposition velocity may also be different.

The value selected for V_d depends on the type of vegetation, usually described as either short (grasses or shrubs) or tall (forests). For particles with an MMED of about 0.5, Hicks (1980) gives values for tall vegetation deposition velocity from 0.1 to 0.4 cm/sec. Lannefors and Hansson (1983) estimated values of 0.2 to 0.5 cm/sec in the particle size range of 0.06 to 2.0 μm in a coniferous forest. For lead, with an MMED of 0.55 μm, they measured a deposition velocity of 0.41.

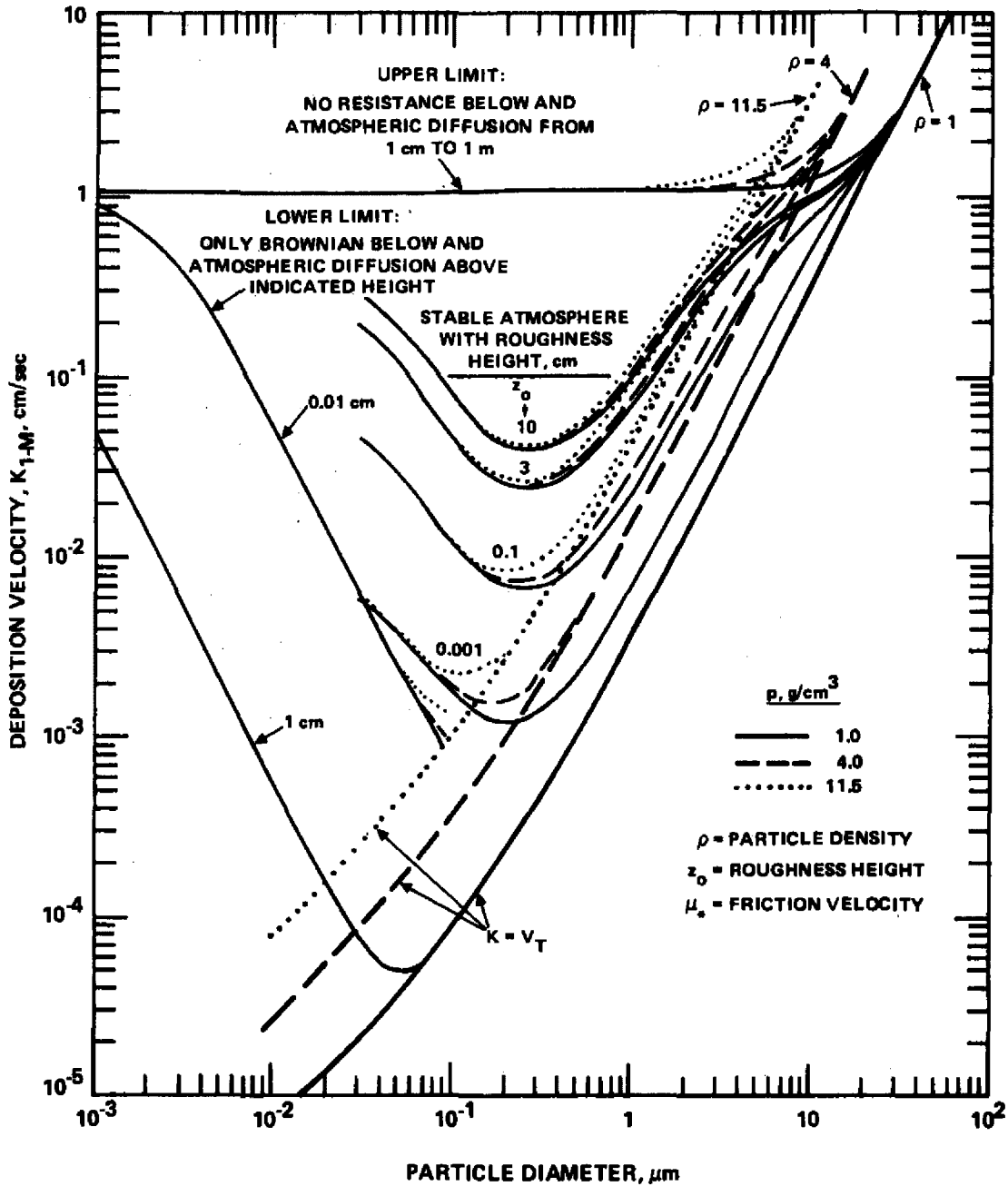

Figure 6-11. Predicted deposition velocities at 1 m for $\mu_* = 30$ cm s^{-1} and particle densities of 1, 4, and 11.5 g cm^{-3}.

Source: Sehmel (1980).

6.4.1.4 Field Measurements of Dry Deposition on Surrogate and Natural Surfaces. Several investigators have used surrogate surface devices similar to those described in Section 4.2.2.4. These data are summarized in Table 6-5. The few studies available on deposition to vegetation surfaces show deposition rates comparable to those of surrogate surfaces and deposition velocities in the range predicted by the models discussed above. In Section 6.4.3, these data are used to show that global emissions are in approximate balance with global deposition. It is reasonable that future refinements of field measurements and model calculations will permit more accurate estimates of dry deposition in specific regions or under specific environmental conditions.

TABLE 6-5. SUMMARY OF SURROGATE AND VEGETATION SURFACE DEPOSITION OF LEAD

Depositional surface	Flux ng Pb/cm^2·day	Air conc ng/m^3	Deposition velocity cm/sec	Reference
Tree leaves (Paris)	0.38	---	0.086	1
Tree leaves (Tennessee)	0.29-1.2	---	---	2
Plastic disk (remote California)	0.02-0.08	13-31	0.05-0.4	3
Plastic plates (Tennessee)	0.29-1.5	110	0.05-0.06	4
Tree leaves (Tennessee)	---	110	0.005	4
Snow (Greenland)	0.004	0.1-0.2	0.1	5
Grass (Pennsylvania)	---	590	0.2-1.1	6
Coniferous forest (Sweden)	0.74	21	0.41	7

1. Servant, 1975.
2. Lindberg et al., 1982.
3. Elias and Davidson, 1980.
4. Lindberg and Harriss, 1981.
5. Davidson et al., 1981.
6. Davidson et al., 1982.
7. Lannefors et al., 1983.

6.4.2 Wet Deposition

Wet deposition includes removal by rainout and washout. Rainout occurs when particulate matter is present in the supersaturated environment of a growing cloud. The small particles (0.1 to 0.2 μm) act as nuclei for the formation of small droplets, which grow into raindrops (Junge, 1963). Droplets also collect particles under 0.1 μm by Brownian motion and by the water-vapor gradient. The nucleation process may also occur on particulate matter present below cloud level, producing droplets large enough to be affected by sedimentation. These processes are referred to as rainout. Washout, on the other hand, occurs when falling raindrops collect particles by diffusion and impaction on the way to the ground. Although data on the lead content of precipitation are rather limited, those that do exist indicate a high variability.

Results on lead scavenging by washout are conflicting. In a laboratory study employing simulated rainfall, Edwards (1975) found that less than 1 percent of auto exhaust lead particles could be removed by washout. However, Ter Haar et al. (1967) found that intense rainfall removed most of the atmospheric lead. As a result, the lead content of rain water is smaller for intense rainfall than in steady showers, presumably because the air contains progressively less lead. It is not clear which of the two phenomena, nucleation or washout, is responsible.

Lazrus et al. (1970) sampled precipitation at 32 U.S. stations and found a correlation between gasoline used and lead concentrations in rainfall in each area. Similarly, there is probably a correlation between lead concentration in rainfall and distance from large stationary point sources. The authors pointed out that at least twice as much lead is found in precipitation as in water supplies, implying the existence of a process by which lead is removed from the soil solution after precipitation reaches the ground. Russian studies (Konovalov et al., 1966) point to the insolubility of lead compounds in surface waters and suggest removal by natural sedimentation and filtration.

Atkins and Kruger (1968) conducted a field sampling program in Palo Alto, California, to determine the effectiveness of sedimentation, impaction, rainout, and washout in removing lead from the atmosphere. Rainfall in the area averages approximately 33 cm/year and occurs primarily during the late fall and winter months. Airborne concentrations at a freeway site varied from 0.3 $\mu g/m^3$ to a maximum of 19 $\mu g/m^3$ in the fall and winter seasons, and were a maximum of 9.3 $\mu g/m^3$ in the spring. During periods of light rainfall in the spring, the maximum concentration observed was 7.4 $\mu g/m^3$. More than 90 percent of the lead reaching the surface during the one-year sampling period was collected in dry fallout. Wet deposition accounted for 5 to 10 percent of the lead removal at the sampling sites.

Andren et al. (1975) evaluated the contribution of wet and dry deposition of lead in a study of the Walker Branch Watershed in Oak Ridge, Tennessee, during the period June 1973 to July 1974. The mean precipitation in the area is approximately 130 cm/yr. Results reported for the period January through June 1974 are presented in Table 6-6. Wet deposition contributed approximately 67 percent of the total deposition for the period.

TABLE 6-6. DEPOSITION OF LEAD AT THE WALKER BRANCH WATERSHED, 1974

Period	Lead deposition (g/ha)	
	Wet	Dry
January	34.1	<16.7
February	6.7	< 3.3
March	21.6	<10.6
April	15.4	< 7.5
May	26.5	<13.0
June	11.1	< 5.4
Total	115.4	56.5
Average	19.2	9.4

[a]Total deposition ~172 g/ha. Wet deposition ~67 percent of total.
Source: Andren et al., 1975.

6.4.3 Global Budget of Atmospheric Lead

The geochemical mass balance of lead in the atmosphere may be determined from quantitative estimates of inputs and outputs. Inputs are from natural and anthropogenic emissions described in Section 5.2 and 5.3. They amount to 450,000 to 475,000 metric tons annually (Nriagu, 1979). There are no published estimates of global deposition from the atmosphere, but the data provided in Sections 6.4.1 and 6.4.2 can provide a reasonable basis on which to make such an estimate. Table 6-7 shows an average concentration of 0.4 µg Pb/kg precipitation. The total mass of rain and snowfall is 5.2×10^7 kg, so the amount of lead removed by wet deposition is approximately 208,000 t/yr. For dry deposition, a crude estimate may be derived by dividing the surface of the Earth into three major vegetation types based on surface roughness or LAI. Oceans, polar regions, and deserts have a very low surface rough-

TABLE 6-7. ESTIMATED GLOBAL DEPOSITION OF ATMOSPHERIC LEAD

	Deposition from atmosphere: Mass 10^{17} kg/yr	Concentration 10^{-6} g/kg	Deposition 10^{6} kg/yr
Wet			
To oceans	4.1	0.4	164
To continents	1.1	0.4	44
Dry	Area 10^{12} km^2	Deposition rate 10^{-3} g/m^2·yr	Deposition 10^{6} kg/yr
To oceans, ice caps, deserts	405	0.2	89
Grassland, agricultural areas, and tundra	46	0.71	33
Forests	59	1.5	80
		Total dry:	202
		Total wet:	208
		Global:	410

Source: This report.

ness and can be assigned a deposition velocity of 0.01 cm/sec, which gives a flux of 0.2 μg/m^2·yr assuming 75 ng Pb/m^3 air concentration. Grasslands, tundra, and other areas of low-lying vegetation have a somewhat higher deposition velocity; forests would have the highest. Values of 0.3 and 0.65 can be assigned to these two vegetation types, based on the data of Davidson et al. (1982). Whittaker (1975) lists the global surface area of each of the three types as 405, 46, and 59 x 10^{12} km^2, respectively. In the absence of data on the global distribution of air concentrations of lead, an average of 0.075 μg/m^3 is assumed. Multiplying air concentration by deposition velocity gives the deposition flux for each vegetation type shown on Table 6-7. The combined wet and dry deposition is 410,000 metric tons, which compares favorably with the estimated 450,000 to 475,000 metric tons of emissions.

distributions represent the most extensive size distribution data base available. However, the impactors were operated at excessive air flow rates that most likely resulted in particle bounceoff, biasing the data toward smaller particles (Dzubay et al., 1976). Many of the later distributions, although obtained by independent investigators with unknown quality control, were collected using techniques which minimize particle bounceoff and hence may be more reliable. It is important to note that a few of the distributions were obtained without backup filters that capture the smallest particles. These distributions are likely to be inaccurate, since an appreciable fraction of the airborne lead mass was probably not sampled. The distributions of Figure 7-5 have been used with published lung deposition data to estimate the fraction of inhaled airborne lead deposited in the human respiratory system (see Chapter 10).

7.2.1.3.2 Vertical gradients and siting guidelines. New guidelines for placing ambient air lead monitors went into effect in July, 1981 (F.R., 1981). "Microscale" sites, placed between 5 and 15 meters from thoroughfares and 2 to 7 meters above the ground, are prescribed, but until now few monitors have been located that close to heavily traveled roadways. Many of these microscale sites might be expected to show higher lead concentrations than that measured at nearby middlescale urban sites, due to vertical gradients in lead concentrations near the source. One study (PEDCo, 1981) gives limited insight into the relationship between a microscale location and locations further from a roadway. The data in Table 7-6 summarize total suspended particulates and particulate lead concentrations in samples collected in Cincinnati, Ohio, on 21 consecutive days in April and May, 1980, adjacent to a 58,500 vehicles-per-day expressway connector. Simple interpolation indicates that a microscale monitor as close as 5 meters from the roadway and 2 meters above the ground would record concentrations some 20 percent higher than those at a "middle scale" site 21.4 meters from the roadway. On the other hand, these data also indicate that although lead concentrations very close to the roadway (2.8 m setback) are quite dependent on the height of the sampler, the averages at the three selected heights converge rapidly with increasing distance from the roadway. In fact, the average lead concentration (1.07 $\mu g/m^3$) for the one monitor (6.3 m height, 7.1 m setback) that satisfies the microscale site definition proves not to be significantly different from the averages for its two companions at 7.1 m, or from the averages for any of the three monitors at the 21.4 m setback. It also appears that distance from the source, whether vertical or horizontal, can be the primary determining factor for changes in air lead concentrations. At 7.1 m from the highway, the 1.1 and 6.3 m samplers would be about 7 and 11 meters from the road surface. The values at these vertical distances are only slightly lower than the corresponding values for comparable horizontal distances.

Mass balance calculations of this type serve to accentuate possible errors in the data which are not otherwise obvious. The data used above are not held to be absolutely firm. Certainly, more refined estimates of air concentrations and deposition velocities can be made in the future. On the other hand, the calculations above show some published calculations to be unreasonable. In particular, values of 36 μg/kg rain reported by Lazrus (1970) would account for more than 50 times the total global emissions. Likewise, deposition fluxes of 0.95 $\mu g/cm^2 \cdot yr$ reported by Jaworowski et al. (1981) would account for 10 times global emissions. Chemical budgets are an effective means of establishing reasonable limits to environmental lead data.

6.5 TRANSFORMATION AND TRANSPORT IN OTHER ENVIRONMENTAL MEDIA

6.5.1 Soil

Soils have both a liquid and solid phase, and trace metals are normally distributed between these two phases. In the liquid phase, metals may exist as free ions or as soluble complexes with organic or inorganic ligands. Organic ligands are typically humic substances such as fulvic or humic acid, and the inorganic ligands may be iron or manganese hydrous oxides. Since lead rarely occurs as a free ion in the liquid phase (Camerlynck and Kiekens, 1982), its mobility in the soil solution depends on the availability of organic or inorganic ligands. The liquid phase of soil often exists as a thin film of moisture in intimate contact with the solid phase. The availability of metals to plants depends on the equilibrium between the liquid and solid phase.

In the solid phase, metals may be incorporated into crystalline minerals of parent rock material, into secondary clay minerals, or precipitated as insoluble organic or inorganic complexes. They may also be adsorbed onto the surfaces of any of these solid forms. Of these categories, the most mobile form is in soil moisture, where lead can move freely into plant roots or soil microorganisms with dissolved nutrients. The least mobile is parent rock material, where lead may be bound within crystalline structures over geologic periods of time. Intermediate are the lead complexes and precipitates. Transformation from one form to another depends on the chemical environment of the soil. For example at pH 6 to 8, insoluble organic-Pb complexes are favored if sufficient organic matter is available; otherwise hydrous oxide complexes may form or the lead may precipitate with the carbonate or phosphate ion. In the pH range of 4 to 6, the organic-Pb complexes become soluble. Soils outside the pH range of 4 to 8 are rare. The interconversion between soluble and insoluble organic complexes affects the equilibrium of lead between the liquid and solid phase of soil.

Even though the equilibrium may shift toward the insoluble form so strongly that 99.9 percent of the lead may be immobilized, 0.01 percent of the lead in total soil can have a significant effect on plants and microorganisms if the soils are heavily contaminated with lead (Chapter 8).

The water soluble and exchangeable forms of metals are generally considered available for plant uptake (Camerlynck and Kiekens, 1982). These authors demonstrated that in normal soils, only a small fraction of the total lead is in exchangeable form (about 1 μg/g) and none exists as free lead ions. Of the exchangeable lead, 30 percent existed as stable complexes, 70 percent as labile complexes. The organic content of these soils was low (3.2 percent clay, 8.5 percent silt, 88.3 percent sand). In heavily contaminated soils near a midwestern industrial site, Miller and McFee (1983) found that 77 percent of the lead was in exchangeable or organic form, although still none could be found in aqueous solution. Soils had a total lead content from 64 to 360 μg/g and an organic content of 7 to 16 percent.

Atmospheric lead may enter the soil system by wet or dry deposition mechanisms described earlier. There is evidence that this lead enters as $PbSO_4$ or is rapidly converted to $PbSO_4$ at the soil surface (Olson and Skogerboe, 1975). Lead sulfate is relatively soluble and thus could remain mobile if not transformed. Lead could be immobilized by precipitation as less soluble compounds [$PbCO_3$, $Pb(PO_4)_2$], by ion exchange with hydrous oxides or clays, or by chelation with humic and fulvic acids. Santillan-Medrano and Jurinak (1975) discussed the possibility that the mobility of lead is regulated by the formation of $Pb(OH)_2$, $Pb_3(PO_4)_2$, $Pb_5(PO_4)_3OH$, and $PbCO_3$. This model, however, did not consider the possible influence of organic matter on lead immobilization. Zimdahl and Skogerboe (1977), on the other hand, found lead varied linearly with cation exchange capacity (CEC) of soil at a given pH, and linearly with pH at a given CEC (Figure 6-12). The relationship between CEC and organic carbon is discussed below.

Some of the possible mechanisms mentioned above can be eliminated by experimental evidence. If surface adsorption on clays plays a major role in lead immobilization, then the capacity to immobilize should vary directly with the surface-to-volume ratio of clay. Two separate experiments using the nitrogen BET method for determining surface area and size fractionation techniques to obtain samples with different surface-to-volume ratios, Zimdahl and Skogerboe (1977) demonstrated that this was not the case. They also showed that precipitation as lead phosphate or lead sulfate is not significant, although carbonate precipitation can be important in soils that are are carbonaceous in nature or to which lime ($CaCO_3$) has been added.

Of the two remaining processes, lead immobilization is more strongly correlated with organic chelation than with iron and manganese oxide formation (Zimdahl and Skogerboe, 1977). It is possible, however, that chelation with fulvic and humic acids is catalyzed by the presence of iron and manganese oxides (Saar and Weber, 1982). This would explain the positive correlation for both mechanisms observed by Zimdahl and Skogerboe (1977). The study of Miller and McFee (1983) discussed above seemed to indicate that atmospheric lead added to soil is distributed to organic matter (43 percent) and ferro-manganese hydrous oxides (39 percent), with 8 percent found in the exchangeable fraction and 10 percent as insoluble precipitates.

If organic chelation is the correct model of lead immobilization in soil, then several features of this model merit further discussion. First, the total capacity of soil to immobilize lead can be predicted from the linear relationship developed by Zimdahl and Skogerboe (1977) (Figure 6-12) based on the equation:

$$N = 2.8 \times 10^{-6} (A) + 1.1 \times 10^{-5} (B) - 4.9 \times 10^{-5}$$

where N is the saturation capacity of the soil expressed in moles/g soil, A is the CEC of the soil in meq/100 g soil, and B is the pH. Because the CEC of soil is more difficult to determine than total organic carbon, it is useful to define the relationship between CEC and organic content. Pratt (1957) and Klemmedson and Jenny (1966) found a linear correlation between CEC and organic carbon for soils of similar sand, silt, and clay content. The data of Zimdahl and Skogerboe (1977) also show this relationship when grouped by soil type. They show that sandy clay loam with an organic content of 1.5 percent might be expected to have a CEC of 12 meq/100 g. From the equation, the saturation capacity for lead in soil of pH 5.5 would be 45 μmoles/g soil or 9,300 μg/g. The same soil at pH 4.0 would have a total capacity of 5,900 μg/g.

The soil humus model also facilitates the calculation of lead in soil moisture using values available in the literature for conditional stability constants with fulvic acid. The term conditional is used to specify that the stability constants are specific for the conditions of the reaction. Conditional stability constants for HA and FA are comparable. The values reported for log K are linear in the pH range of 3 to 6 (Buffle and Greter, 1979; Buffle et al., 1976; Greter et al., 1979), so that interpolations in the critical range of pH 4 to 5.5 are possible (Figure 6-12). Thus, at pH 4.5, the ratio of complexed lead to ionic lead is expected to be 3.8×10^3. For soils of 100 μg/g, the ionic lead in soil moisture solution would be 0.03 μg/g. The significance of this ratio is discussed in Section 8.2.1.

It is also important to consider the stability constant of the Pb-FA complex relative to other metals. Schnitzer and Hansen (1970) showed that at pH 3, Fe^{3+} is the most stable in the

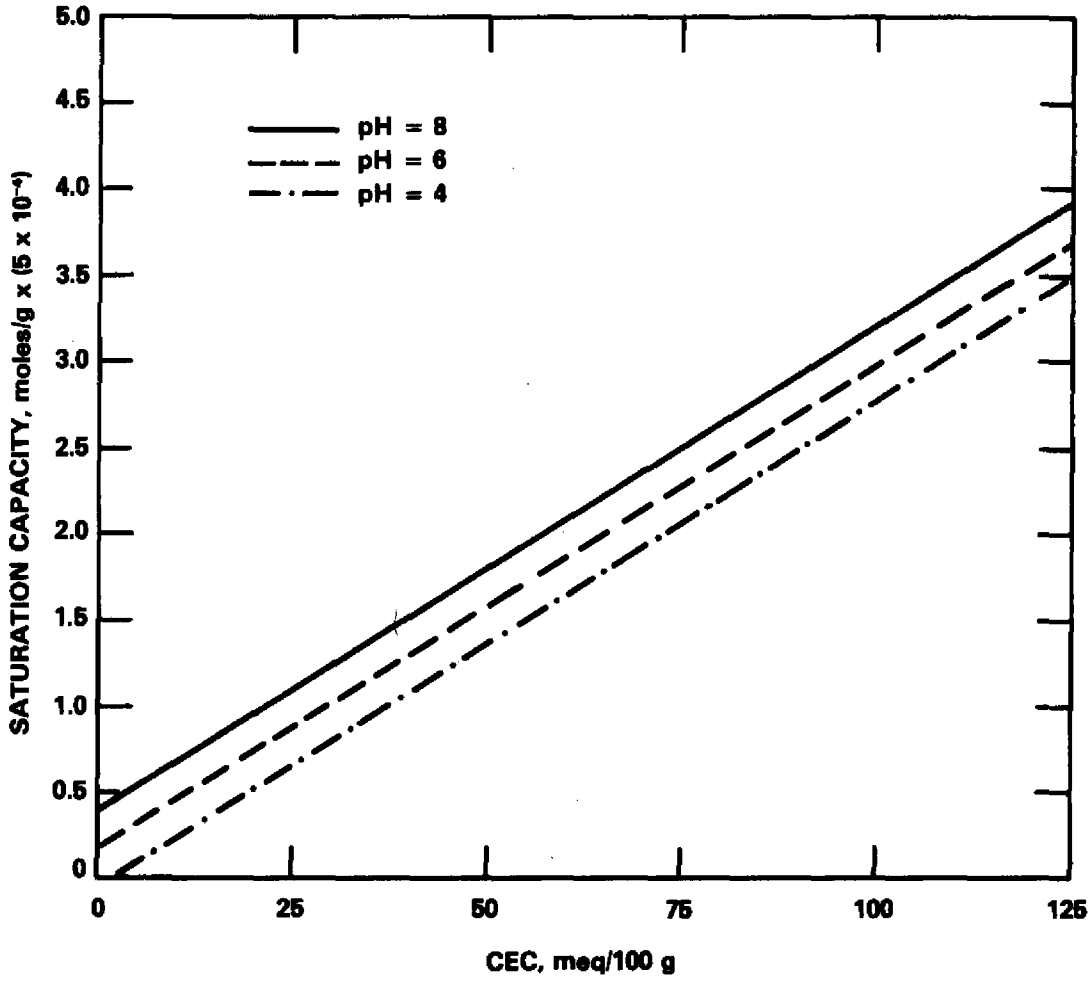

Figure 6-12. Variation of lead saturation capacity with cation exchange capacity in soil at selected pH values.

Source: Data from Zimdahl and Skogerboe (1977).

sequence $Fe^{3+} > Al^{3+} > Cu^{2+} > Ni^{2+} > Co^{2+} > Pb^{2+} > Ca^{2+} > Zn^{2+} > Mn^{2+} > Mg^{2+}$. At pH 5, this sequence becomes $Ni^{2+} = Co^{2+} > Pb^{2+} > Cu^{2+} > Zn^{2+} = Mn^{2+} > Ca^{2+} > Mg^{2+}$. This means that at normal soil pH levels of 4.5 to 8, lead is bound to FA + HA in preference to many other metals that are known plant nutrients (Zn, Mn, Ca, and Mg). Furthermore, if lead displaces iron in this scheme, an important function of FA may be inhibited at near saturation capacity. Fulvic acid is believed to play a role in the weathering of parent rock material by the removal of iron from the crystalline structure of the minerals, causing the rock to weather more rapidly. In the absence of this process, the weathering of parent rock material and the subsequent release of nutrients to soil would proceed more slowly.

6.5.2 Water

6.5.2.1 Inorganic. The chemistry of lead in an aqueous solution is highly complex because the element can be found in a multiplicity of forms. Hem and Durum (1973) have reviewed the chemistry of lead in water in detail; the aspects of aqueous lead chemistry that are germane to this document are discussed in Section 3.3.

Lead in ore deposits does not pass easily to ground or surface water. Any lead dissolved from primary lead sulfide ore tends to combine with carbonate or sulfate ions to (1) form insoluble lead carbonate or lead sulfate, or (2) be absorbed by ferric hydroxide (Lovering, 1976). An outstanding characteristic of lead is its tendency to form compounds of low solubility with the major anions of natural water. Hydroxide, carbonate, sulfide, and more rarely sulfate may act as solubility controls in precipitating lead from water. The amount of lead that can remain in solution is a function of the pH of the water and the dissolved salt content. Equilibrium calculations show that at pH > 5.4, the total solubility of lead in hard water is about 30 µg/l and about 500 µg/l in soft water (Davies and Everhard, 1973). Lead sulfate is present in soft water and limits the lead concentration in solution. Above pH 5.4, $PbCO_3$ and $Pb_2(OH)_2CO_3$ limit the concentration. The carbonate concentration is in turn dependent on the partial pressure of CO_2 as well as the pH. Calculations by Hem and Durum (1973) show that many river waters in the United States have lead concentrations near the solubility limits imposed by their pH levels and contents of dissolved CO_2. Because of the influence of temperature on the solubility of CO_2, observed lead concentrations may vary significantly from theoretically calculated ones.

Lazrus et al. (1970) calculated that as much as 140 g/ha·mo of lead may be deposited by rainfall in some parts of the northeastern United States. Assuming an average annual rainfall runoff of 50 cm, the average concentration of lead in the runoff would have to be about 330 µg/l to remove the lead at the rate of 140 g/ha·mo. Concentrations as high as 330 µg/l

could be stable in water with pH near 6.5 and an alkalinity of about 25 ng bicarbonate ion/l of water. Water having these properties is common in runoff areas of New York State and New England; hence, the potential for high lead concentrations exists there. In other areas, the average pH and alkalinity are so high that maximum concentrations of lead of about 1 µg/l could be retained in solutions at equilibrium (Lovering, 1976).

A significant fraction of the lead carried by river water may be in an undissolved state. This insoluble lead can consist of colloidal particles in suspension or larger undissolved particles of lead carbonate, -oxide, -hydroxide, or other lead compounds incorporated in other components of particulate lead from runoff; it may occur either as sorbed ions or surface coatings on sediment mineral particles or be carried as a part of suspended living or nonliving organic matter (Lovering, 1976). A laboratory study by Hem (1976) of sorption of lead by cation exchange indicated that a major part of the lead in stream water may be adsorbed on suspended sediment. Figure 6-13 illustrates the distribution of lead outputs between filtrate and solids in water from both urban and rural streams, as reported by Rolfe and Jennett (1975). The majority of lead output is associated with suspended solids in both urban and rural streams, with very little dissolved in the filtrate. The ratio of lead in suspended solids to lead in filtrate varies from 4:1 in rural streams to 27:1 in urban streams.

Soluble lead is operationally defined as that fraction which is separated from the insoluble fraction by filtration. However, most filtration techniques do not remove all colloidal particles. Upon acidification of the filtered sample, which is usually done to preserve it before analysis, the colloidal material that passed through the filter is dissolved and is reported as dissolved lead. Because the lead in rainfall can be mainly particulate, it is necessary to obtain more information on the amounts of lead transported in insoluble form (Lovering, 1976) before a valid estimate can be obtained of the effectiveness of runoff in transporting lead away from areas where it has been deposited by atmospheric fallout and rain.

6.5.2.2 Organic. The bulk of organic compounds in surface waters originates from natural sources. (Neubecker and Allen, 1983). The humic and fulvic acids that are primary complexing agents in soils are also found in surface waters at concentrations from 1 to 5 mg/l, occasionally exceeding 10 mg/l. (Steelnik, 1977), and have approximately the same chemical characteristics (Reuter and Perdue, 1977). The most common anthropogenic organic compounds are NTA and EDTA (Neubecker and Allen, 1983). There are many other organic compounds such as oils, plasticizers, and polymers discharged from manufacturing processes that may complex with lead.

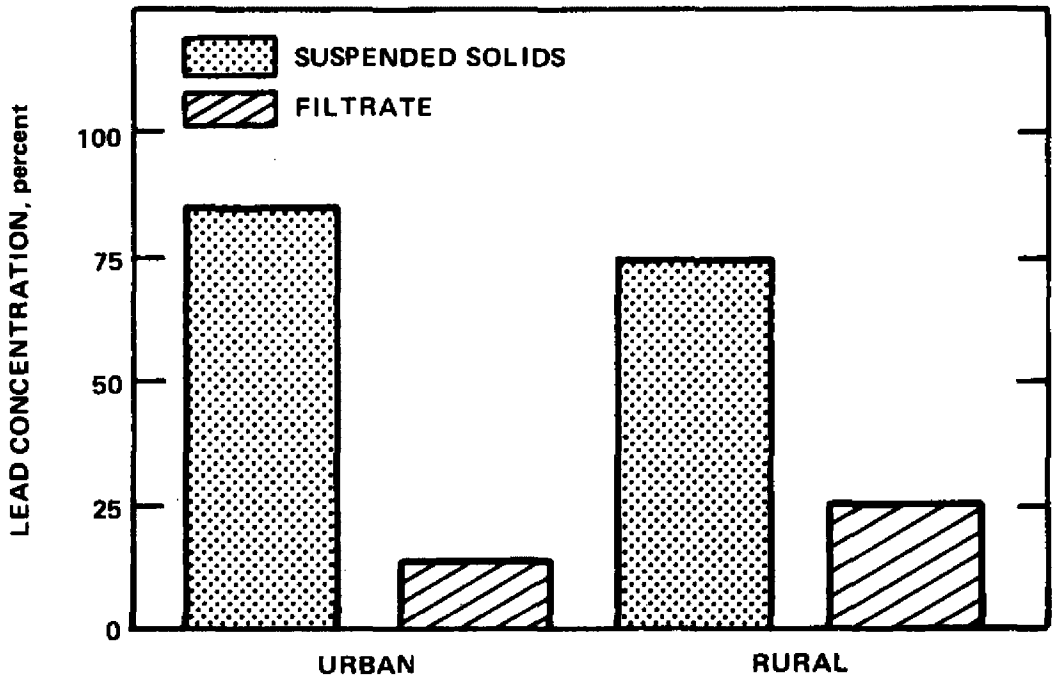

Figure 6-13. Lead distribution between filtrate and suspended solids in stream water from urban and rural compartments.

Source: Hem (1976); Rolfe and Jennett (1975).

The presence of fulvic acid in water has been shown to increase the rate of solution of lead sulfide 10 to 60 times over that of a water solution at the same pH that did not contain fulvic acid (Bondarenko, 1968; Lovering, 1976). At pH values near 7, soluble lead-fulvic acid complexes are present in solution. At initial pH values between 7.4 and about 9, the lead-fulvic acid complexes are partially decomposed, and lead hydroxide and carbonate are precipitated. At initial pH values of about 10, the lead-fulvic acid complexes again increase. This increase is attributed to dissociation of phenolic groups at high pH values, which increases the complexing capacity of the fulvic acid. But it also may be due to the formation of soluble lead-hydroxyl complexes.

The transformation of inorganic lead, especially in sediment, to tetramethyllead (TML) has been observed and biomethylation has been postulated (Schmidt and Huber, 1976; Wong et al., 1975). However, Reisinger et al. (1981) have reported extensive studies of the methylation of lead in the presence of numerous bacterial species known to alkylate mercury and other heavy metals. In these experiments no biological methylation of lead was found under any condition. Chemical alkylation from methylcobalamine was found to occur in the presence of sulfide or of aluminum ion; chemical methylation was independent of the presence of bacteria.

Jarvie et al. (1977, 1981) have recently shown that tetraalkyllead (TEL) compounds are unstable in water. Small amounts of Ca^{2+} and Fe^{2+} ions and sunlight have been shown to cause decomposition of TEL over time periods of 5 to 50 days. The only product detected was triethyllead, which appears to be considerably more stable than the TEL. Tetramethyllead is decomposed much more rapidly than TEL in water, to form the trimethyl lead ion. Initial concentrations of 10^{-4} molar were reduced by one order of magnitude either in the dark or light in one day, and were virtually undetectable after 21 days. Apparently, chemical methylation of lead to the trialkyllead cation does occur in some water systems, but evolution of TML appears insignificant.

Lead occurs in riverine and estuarial waters and alluvial deposits. Laxen and Harrison (1977) and Harrison and Laxen (1981) found large concentrations of lead (~1 mg/l) in rainwater runoff from a roadway; but only 5 to 10 percent of this is soluble in water. Concentrations of lead in ground water appear to decrease logarithmically with distance from a roadway. Rainwater runoff has been found to be an important transport mechanism in the removal of lead from a roadway surface in a number of studies (Bryan, 1974; Harrison and Laxon, 1981; Hedley and Lockley, 1975; Laxen and Harrison, 1977).

Apparently, only a light rainfall, 2 to 3 mm, is sufficient to remove 90 percent of the lead from the road surface to surrounding soil and to waterways (Laxen and Harrison, 1977).

The Applied Geochemistry Research Group (1978) has reported elevated lead concentrations (40 µg/g and above) in about 30 percent of stream bed sediment samples from England and Wales in a study of 50,000 such samples. Abdullah and Royle (1973) have reported lead levels in coastal areas of the Irish sea of 400 µg/g and higher.

Evidence for the sedimentation of lead in freshwater streams may be found in several reports. Laxen and Harrison (1983) found that lead in the effluent of a lead-acid battery plant near Manchester, England, changed drastically in particle size. In the plant effluent, 53 percent of the lead was on particles smaller than 0.015 µm and 43 percent on particles greater than 1 µm. Just downstream of the plant, 91 percent of the lead was on particles greater than 1 µm and only 1 percent on particles smaller than 0.015 µm. Under these conditions, lead formed or attached to large particles at a rate exceeding that of Cd, Cu, Fe or Mn.

The lead concentrations in off-shore sediments often show a marked increase corresponding to anthropogenic activity in the region (Section 5.1). Rippey et al. (1982) found such increases recorded in the sediments of Lough Neagh, Northern Ireland, beginning during the 1600's and increasing during the late 1800's. Corresponding increases were also observed for Cr, Cu, Zn, Hg, P, and Ni. For lead, the authors found an average anthropogenic flux of 72 $mg/m^2 \cdot yr$, of which 27 $mg/m^2 \cdot yr$ could be attributed to direct atmospheric deposition. Prior to 1650, the total flux was 12 $mg/m^2 \cdot yr$, so there has been a 6-fold increase since that time.

Ng and Patterson (1982) found prehistoric fluxes of 1 to 7 mg $Pb/m^2 \cdot yr$ to three offshore basins in southern California, which have now increased 3 to 9-fold to 11 to 21 $mg/m^2 \cdot yr$. Much of this lead is deposited directly from sewage outfalls, although at least 25 percent probably comes from the atmosphere.

6.5.3 Vegetation Surfaces

The deposition of lead on the leaf-surfaces of plants where the particles are often retained for a long time must also be considered (Dedolph et al., 1970; Gange and Joshi, 1971; Schuck and Locke, 1970). Several studies have shown that plants near roadways exhibit considerably higher levels of lead than those further away. In most instances, the higher concentrations were due to lead particle deposition on plant surfaces (Schuck and Locke, 1970). Studies have shown that particles deposited on plant surfaces are difficult to remove by typical kitchen washing techniques. (Arvik and Zimdahl, 1974; Gange and Joshi, 1971; Lagerwerff et al., 1973). Leaves with pubescent surfaces seem able to attract and retain

particles via an electrostatic mechanism.. Other types of leaves are covered with a cuticular wax sufficiently sticky to retain particles. Thus, rainfall does not generally remove the deposited particles (Arvik and Zimdahl, 1974). Animals or humans consuming the leafy portions of such plants can certainly be exposed to higher than normal levels of lead. Fortunately, a major fraction of lead emitted by automobiles tends to be deposited inside a highway right-of-way, so at least part of this problem is alleviated.

The particle deposition on leaves has led some investigators to stipulate that lead may enter plants through the leaves. This would typically require, however, that the lead particles be dissolved by constituents of the leaf surface and/or converted to the ionic form via contact with water. The former possibility is not considered likely since cuticular waxes are relatively chemically inert. Arvik and Zimdahl (1974) have shown that entry of ionic lead through plant leaves is of minimal importance. Using the leaf cuticles of several types of plants essentially as dialysing membranes, they found that even high concentrations of lead ions would not pass through the cuticles into distilled water on the opposite side.

The uptake of soluble lead by aquatic plants can be an important mechanism for depleting lead concentrations in downstream waterways. Gale and Wixson (1979) have studied the influence of algae, cattails, and other aquatic plants on lead and zinc levels in wastewater in the New Lead Belt of Missouri. These authors report that mineral particles become trapped by roots, stems, and filaments of aquatic plants. Numerous anionic sites on and within cell walls participate in cation exchange, replacing metals such as lead with Na^+, K^+, and H^+ ions. Mineralization of lead in these Missouri waters may also be promoted by water alkalinity. However, construction of stream meanders and settling ponds have greatly reduced downstream water concentrations of lead, mainly because of absorption in aquatic plants (Gale and Wixson, 1979).

6.6 SUMMARY

From the source of emission to the site of deposition, lead particles are dispersed by the flow of the airstream, transformed by physical and chemical processes, and removed from the atmosphere by wet or dry deposition. Under the simplest of conditions (smooth, flat terrain), the dispersion of lead particles has been modeled and can be predicted (Benarie, 1980). Dispersion modeling in complex terrains is still under development and these models have not been evaluated (Kotake and Sano, 1981).

Air lead concentrations decrease logarithmically away from roadways (Edwards, 1975) and smelters (Roberts et al., 1974). Within urban regions, air concentrations decrease from the central business district to the outlying residential areas by a factor of 2 to 3. In moving

from urban to rural areas, air concentrations decrease from 1 to 2 $\mu g/m^3$ down to 0.1 to 0.5 $\mu g/m^3$ (Chapter 7). This decrease is caused by dilution with clean air and removal by deposition. During dispersion to remote areas, concentrations decrease to 0.01 $\mu g/m^3$ in the United States (Elias and Davidson, 1980), to 0.001 $\mu g/m^3$ in the Atlantic Ocean (Duce et al., 1975), and to 0.000076 $\mu g/m^3$ in Antarctica (Maenhaut et al., 1979).

Physical transformations of lead particles cause a shift in the particle size distribution. The bimodal distribution of large and small particles normally found on the roadway changes to a single mode of intermediate sized particles with time and distance (Huntzicker et al., 1975). This is probably because large particles deposit near roadways and small particles agglomerate to medium sized particles with an MMED of about 0.2 to 0.3 μm.

Particles transform chemically from lead halides to lead sulfates and oxides. Organolead compounds usually constitute 1 to 6 percent of the total airborne lead in ambient urban air (Harrison et al., 1979).

Wet deposition accounts for about half of the removal of lead particles from the atmosphere. The mechanisms may be rainout, where the lead may be from another region, or washout, where the source may be local. The other half of the atmospheric lead is removed by dry deposition. Mechanisms may be gravitational for large particles or a combination of gravitational and wind-related mechanisms for small particles (Elias and Davidson, 1980). Models of dry deposition predict deposition velocities as a function of particle size, windspeed, and surface roughness. Because of their large surface area/ground area ratio, vegetation surfaces receive the bulk of dry deposited particles over continental areas. Wet and dry deposition account for the removal of over 400,000 t/year of the estimated 450,000 t/yr emissions (Nriagu, 1979).

Lead enters soil as a moderately insoluble lead sulfate and is immobilized by complexation with humic and fulvic acids. This immobilization is a function of pH and the concentration of humic substances. At low pH (~4) or low organic content (<5 percent), immobilization of lead in soil may be limited to a few hundred μg/g (Zimdahl and Skogerboe, 1977), but at 20 percent organic content and pH 6, 10,000 μg Pb/g soil may be found.

In natural waters, lead may precipitate as lead sulfate or carbonate, or it may form a complex with ferric hydroxide (Lovering, 1976). The solubility of lead in water is a function of pH and hardness (a combination of Ca and Mg content). Below pH 5.4, concentrations of dissolved lead may vary from 30 μg/l in hard water to 500 μg/l in soft water at saturation (Lovering, 1976).

Particles deposited by dry deposition on vegetation surfaces (leaves and bark) are retained for the lifetime of the plant part. The particles are not easily washed off by rain nor are they taken up directly by the leaf (Arvik and Zimdahl, 1974).

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7. ENVIRONMENTAL CONCENTRATIONS AND POTENTIAL PATHWAYS TO HUMAN EXPOSURE

7.1 INTRODUCTION

In general, typical levels of human lead exposure may be attributed to four components of the human environment: food, inhaled air, dusts of various types, and drinking water. This chapter presents information on the ranges and temporal trends of concentrations in ambient air, soil, and natural waters, and discusses the pathways from each source to food, inhaled air, dust, and drinking water. The ultimate goal is to quantify the contribution of anthropogenic lead to each source and the contribution of each source to the total lead consumed by humans. These sources and pathways of human lead exposure are diagrammed in Figure 7-1.

Chapters 5 and 6 discuss the emission, transport, and deposition of lead in ambient air. Some information is also presented in Chapter 6 on the accumulation of lead in soil and on plant surfaces. Because this accumulation is at the beginning of the human food chain, it is critical to understand the relationship between this lead and lead in the human diet. It is also important where possible to project temporal trends.

In this chapter, a baseline level of potential human exposure is determined for a normal adult eating a typical diet and living in a non-urban community. This baseline exposure is deemed to be unavoidable by any reasonable means. Beyond this level, additive exposure factor s can be determined for other environments (e.g., urban, occupational, smelter communities), for certain habits and activities (e.g., pica, smoking, drinking, and hobbies), and for variations due to age, sex, or socioeconomic status.

7.2 ENVIRONMENTAL CONCENTRATIONS

Quantifying human exposure to lead requires an understanding of ambient lead levels in environmental media. Of particular importance are lead concentrations in ambient air, soil, and surface or ground water. The following sections discuss environmental lead concentrations in each of these media in the context of anthropogenic vs. natural origin, and the contribution of each to potential human exposure.

7.2.1 Ambient Air

Ambient airborne lead concentrations may influence human exposure through direct inhalation of lead-containing particles and through ingestion of lead which has been deposited from the air onto surfaces. Although a plethora of data on airborne lead is now available, our understanding of the pathways to human exposure is far from complete because most ambient measurements were not taken in conjunction with studies of the concentrations of lead in man or in components of his food chain. However, that is the context in which these studies must now

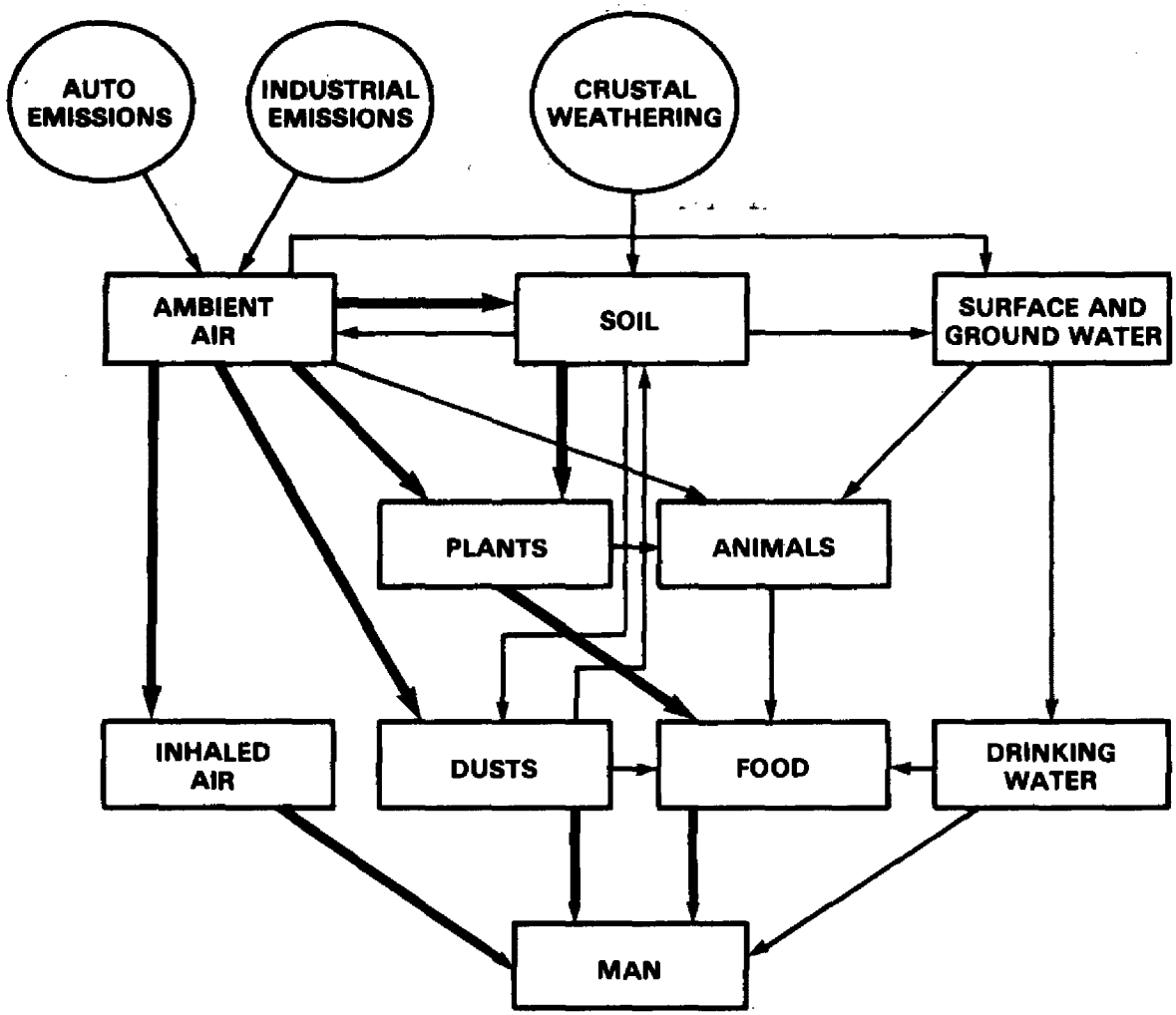

Figure 7-1. Pathways of lead from the environment to human consumption. Heavy arrows are those pathways discussed in greatest detail in this chapter.

be interpreted to shed the most light possible on the concentrations likely to be encountered in various environmental settings.

The most complete set of data on ambient air concentrations may be extracted from the National Filter Analysis Network (NFAN) and its predecessors (see Section 4.2.1). These data, which are primarily for urban regions, have been supplemented with published data from rural and remote regions of the United States. Because some stations in the network have been in place for about 15 years, information on temporal trends is available but sporadic. Ambient air concentrations in the United States are comparable to other industrialized nations. In remote regions of the world, air concentrations are two or three orders of magnitude lower, lending credence to estimates of the concentration of natural lead in the atmosphere. In the context of the NFAN data base, the conditions are considered which modify ambient air, as measured by the monitoring networks, to air as inhaled by humans. Specifically, these conditions are changes in particle size distributions, changes with vertical distance above ground, and differences between indoor and outdoor concentrations.

7.2.1.1 Total Airborne Lead Concentrations. A thorough understanding of human exposure to airborne lead requires detailed knowledge of spatial and temporal variations in ambient concentrations. The wide range of concentrations is apparent from Table 7-1, which summarizes data obtained from numerous independent measurements. Concentrations vary from 0.000076 $\mu g/m^3$ in remote areas to over 10 $\mu g/m^3$ near sources such as smelters. Many of the remote areas are far from human habitation and therefore do not reflect human exposure. However, a few of the regions characterized by low lead concentrations are populated by individuals with primitive lifestyles; these data provide baseline airborne lead data to which modern American lead exposures can be compared. Examples include some of the data from South America and the data from Nepal.

Urban, rural, and remote airborne lead concentrations in Table 7-1 suggest that human exposure to lead has increased as the use of lead in inhabited areas has increased. This is consistent with published results of retrospective human exposure studies. For example, Ericson et al. (1979) have analyzed the teeth and bones of Peruvians buried 1600 years ago. Based on their data, they estimate that the skeletons of present-day American and British adults contain roughly 500 times the amount of lead which would occur naturally in the absence of widespread anthropogenic lead emissions. Grandjean et al. (1979) and Shapiro et al. (1980) report lead levels in teeth and bones of contemporary populations to be elevated 100-fold over levels in ancient Nubians buried before 750 A.D. On the other hand, Barry and Connolly (1981) report excessive lead concentrations in buried medieval English skeletons; one cannot discount the possibility that the lead was absorbed into the skeletons from the surrounding soil.

TABLE 7-1. ATMOSPHERIC LEAD IN URBAN, RURAL, AND REMOTE AREAS OF THE WORLD

Location	Sampling period	Lead conc. ($\mu g/m^3$)	Reference
Urban			
Miami	1974	1.3	HASL, 1975
New York	1978-79	1.1	see Table 7-3
Boston	1978-79	0.8	see Table 7-3
St. Louis	1973	1.1	see Table 7-3
Houston	1978-79	0.9	see Table 7-3
Chicago	1979	0.8	see Table 7-3
Salt Lake City	1974	0.89	HASL, 1975
Los Angeles	1978-79	1.4	see Table 7-3
Ottowa	1975	1.3	NAPS, 1975
Toronto	1975	1.3	NAPS, 1975
Montreal	1975	2.0	NAPS, 1975
Berlin	1966-67	3.8	Blokker, 1972
Vienna	1970	2.9	Hartl and Resch, 1973
Zurich	1970	3.8	Högger, 1973
Brussels	1978	0.5	Roels et al., 1980
Turin	1974-79	4.5	Facchetti and Geiss, 1982
Rome	1972-73	4.5	Colacino and Lavagnini, 1974
Paris	1964	4.6	Blokker, 1972
Rio de Janeiro	1972-73	0.8	Branquinho and Robinson, 1976
Rural			
New York Bight	1974	0.13	Duce et al., 1975
Framingham, MA	1972	0.9	O'Brien et al., 1975
Chadron, NE	1973-74	0.045	Struempler, 1975
United Kingdom	1972	0.13	Cawse, 1974
Italy	1976-80	0.33	Facchetti and Geiss, 1982
Belgium	1978	0.37	Roels et al. 1980
Remote			
White Mtn., CA	1969-70	0.008	Chow et al., 1972
High Sierra, CA	1976-77	0.021	Elias and Davidson, 1980
Olympic Nat. Park, WA	1980	0.0022	Davidson et al., 1982
Antarctica	1971	0.0004	Duce, 1972
South Pole	1974	0.000076	Maenhaut et al., 1979
Thule, Greenland	1965	0.0005	Murozumi et al., 1969
Thule, Greenland	1978-79	0.008	Heidam, 1981
Prins Christian-sund, Greenland	1978-79	0.018	Heidam, 1981
Dye 3, Greenland	1979	0.00015	Davidson et al., 1981c
Eniwetok, Pacific Ocean	1979	0.00017	Settle and Patterson, 1982
Kumjung, Nepal	1979	0.00086	Davidson et al., 1981b
Bermuda	1973-75	0.0041	Duce et al., 1976
Spitsbergen	1973-74	0.0058	Larssen, 1977

Source: Updated from Nriaga, 1978

The remote area concentrations reported in Table 7-1 do not necessarily reflect natural, preindustrial lead. Murozumi et al. (1969) and Ng and Patterson (1981) have measured a 200-fold increase over the past 3000 years in the lead content of Greenland snow. In the opinion of the authors, this lead originates in populated mid-latitude regions, and is transported over thousands of kilometers through the atmosphere to the Arctic. All of the concentrations in Table 7-1, including values for remote areas, have been influenced by anthropogenic lead emissions.

Studies referenced in Table 7-1 are limited in that the procedures for determining the quality of the data are generally not reported. In contrast, the two principal airborne lead data bases described in Section 4.2.1 include measurements subjected to documented quality assurance procedures. The U.S. Environmental Protection Agency's National Filter Analysis Network (NFAN) provides comprehensive nationwide data on long-term trends. The second data base, EPA's National Aerometric Data Bank, contains information contributed by state and local agencies, which monitor compliance with the current ambient airborne standard for lead (1.5 $\mu g/m^3$ averaged over a calendar quarter) promulgated in 1978.

7.2.1.1.1 Distribution of air lead in the United States. Figure 7-2 categorizes the urban sites with valid annual averages (4 valid quarters) into several annual average concentration ranges (Akland, 1976; Shearer et al. 1972; U.S. Environmental Protection Agency, 1978, 1979; Quarterly averages of lead from NFAN, 1982). Nearly all of the sites reported annual averages below 1.0 $\mu g/m^3$. Although the decreasing number of monitoring stations in service in recent years could account for some of the shift in averages toward lower concentrations, trends at individual urban stations, discussed below, confirm the apparent national trend of decreasing lead concentration.

The data from these networks show both the maximum quarterly average to reflect compliance of the station to the ambient airborne standard (1.5 $\mu g/m^3$), and quarterly averages to show trends at a particular location. Valid quarterly averages must include at lease five 24-hour sampling periods evenly spaced throughout the quarter. The number of stations complying with the standard has increased, the quarterly averages have decreased, and the maximum 24-hour values appear to be smaller since 1977.

Table 7-2 provides cumulative frequency distributions of all quarterly lead concentrations for urban NFAN stations (1st quarter = Jan-Mar, etc.). Samples collected by the NFAN from 1970 through 1976 were combined for analysis into quarterly composites. Since 1977, the 24-hour samples have been analyzed individually and averaged arithmetically to determine the quarterly average. These data show that the average lead concentration has dropped markedly since 1977. An important factor in this evaluation is that the number of reporting stations has also decreased since 1977. Stations may be removed from the network for several

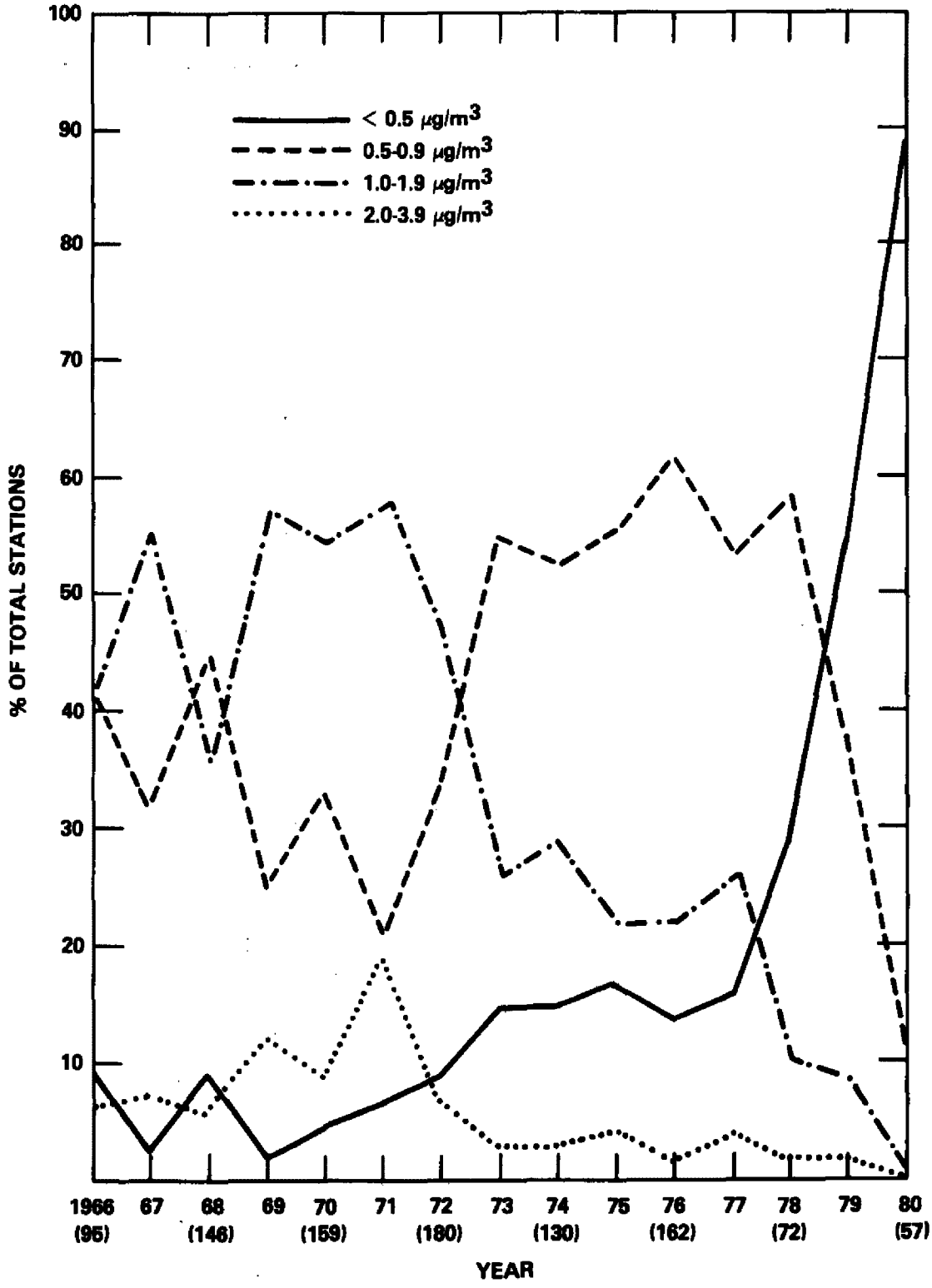

Figure 7-2. Percent of urban stations reporting indicated concentration interval.

TABLE 7-2. CUMULATIVE FREQUENCY DISTRIBUTIONS OF URBAN AIR LEAD CONCENTRATIONS*

Year	No. of Station Reports	Percentile							Max. Qtrly. Avg	Arithmetic		Geometric	
		10	30	50	70	90	95	99		Mean	Std. dev.	Mean	Std. dev.
1970	797	0.47	0.75	1.05	1.37	2.01	2.59	4.14	5.83	1.19	0.80	0.99	1.80
1971	717	0.42	0.71	1.01	1.42	2.21	2.86	4.38	6.31	1.23	0.87	1.00	1.89
1972	708	0.46	0.72	0.97	1.25	1.93	2.57	3.69	6.88	1.13	0.78	0.93	1.87
1973	559	0.35	0.58	0.77	1.05	1.62	2.08	3.03	5.83	0.92	0.64	0.76	1.87
1974	594	0.36	0.57	0.75	1.00	1.61	1.97	3.16	4.09	0.89	0.57	0.75	1.80
1975	695	0.37	0.58	0.78	0.96	1.54	2.02	3.15	4.94	0.89	0.59	0.74	1.82
1976	670	0.37	0.58	0.74	0.96	1.41	1.72	3.07	4.54	0.85	0.55	0.72	1.80
1977	533	0.37	0.57	0.75	0.95	1.67	2.13	3.29	3.96	0.91	0.80	0.68	1.79
1978	282	0.27	0.43	0.57	0.74	1.19	1.49	2.40	3.85	0.68	0.64	0.50	1.87
1979	167	0.22	0.33	0.43	0.63	1.09	1.33	2.44	3.59	0.56	0.58	0.39	1.89
1980	220	0.14	0.21	0.30	0.38	0.55	0.66	0.84	1.06	0.32	0.27	0.24	1.88

*The data reported here are all valid quarterly averages reported from urban stations from 1970 to 1980, in $\mu g/m^3$. The vertical line marks compliance with the 1978 1.5 $\mu g/m^3$ EPA National Ambient Air Quality Standard. In 1980, the quarterly average for all but the highest 1 percent of the stations was 0.84. The sources of the data are Akland, 1976; U.S. EPA, 1978, 1979; Quarterly averages of lead from NFAN, 1982.

reasons, the most common of which is that the locality has now achieved compliance status and fewer monitoring stations are required. It is likely that none of the stations removed from the network were in excess of 1.5 $\mu g/m^3$, and that most were below 1.0 $\mu g/m^3$.

The summary percentiles and means for urban stations (Table 7-2) have decreased over the period from 1970 to 1980, with most of the decrease occurring since 1977; the 1980 levels are in the range of one-third to one-fourth of the values in 1970. The data from non-urban locations are given in Appendix 7A. While the composite nonurban lead concentrations are approximately one-seventh of the urban concentrations, they exhibit the same relative decrease over the 1979-1980 period as the urban sites.

Long-term trends and seasonal variations in airborne lead levels at urban sites can be seen in Figure 7-3. The 10th, 50th, and 90th percentile concentrations are graphed, using quarterly composite and quarterly average data from an original group of 92 urban stations (1965-1974) updated with data for 1975 through 1980. Note that maximum lead concentrations typically occur in the winter, while minima occur in the summer. In contrast, automotive emissions of lead would be expected to be greater in the summer for two reasons: (1) gasoline usage is higher in the summer, and (2) lead content is raised in summer gasolines to replace some of the more volatile high-octane components that cannot be used in summertime gasolines. The effect is apparently caused by the seasonal pattern of lower dispersion capacity in winter, higher capacity in summer.

Figure 7-3 also clearly portrays the significant decrease in airborne lead levels over the past decade. This trend is attributed to the decreasing lead content of regular and premium gasoline, and to the increasing usage of unleaded gasoline. The close parallel between these two parameters is discussed in detail in Chapter 5. (See Figure 5-4 and Table 5-6.)

The decrease in lead concentrations, particularly in 1979 and 1980, was not caused by the disappearance from the network of monitoring sites with characteristically high concentrations; the quarterly values for sites in six cities representing the east coast, the central, and the western sections of the country (Figure 7-4) indicate that the decrease is widespread and real.

Table 7-3 shows lead concentrations in the atmospheres of several major metropolitan areas of epidemiological interest. Some of the data presented do not meet the stringent requirements for quarterly averages and occasionally there have been changes in site location or sampling methodology. Nevertheless, the data are the best available for reporting the history of lead contamination in these specific urban atmospheres. Further discussions of these data appear in Chapter 11.

TABLE 7-3. AIR LEAD CONCENTRATIONS IN MAJOR METROPOLITAN AREAS ($\mu g/m^3$) (quarterly averages)

		Boston MA	New York NY	Phila. PA		Wash. DC	Detroit MI	Chicago IL			Houston TX		Dallas/Ft.Worth TX			Los Angeles CA	
Station	Type	1	1	1	4	1	1	1	2	3	1	4	1	2	4	1	2
Year	Quarter																
1970	1	0.8	1.2			0.9	1.2				1.8		3.8			5.7	3.2
	2		1.5			0.9	1.4				2.0		2.3			3.5	2.2
	3	1.2	1.9				1.4				1.9		2.8			5.1	3.3
	4	1.2	1.4			1.2	1.3				2.5		3.7			3.9	1.9
1971	1		1.6			1.1	1.0				1.9		3.4			6.0	
	2	0.7	1.8			1.3	1.8				1.6		1.8			2.9	
	3					1.3	1.6				1.7		2.5			3.3	
	4		1.7			2.1	2.2				2.7		2.7			6.3	
1972	1	1.0	0.9			1.7					2.3		3.4			3.1	
	2	0.6	1.3			1.2					1.0		1.8			2.0	1.6
	3	2.5	1.0								0.9		2.2			2.6	1.5
	4		1.1			1.1					2.3		2.8			4.7	2.1
1973	1										2.9		1.9			2.7	1.6
	2		0.8								1.8		1.3			2.0	2.5
	3	0.6	1.3								1.7					2.7	
	4		0.9								1.7		1.9				
1974	1		0.5			0.5					1.8		1.3			1.9	1.6
	2	0.9	1.1								2.0	0.6a	1.4	0.2a		2.0	1.7
	3	1.0	0.9				0.9				1.8	0.6	2.8	0.4		1.4	1.9
	4		0.9				0.9				2.6	0.5	3.3	0.6		3.2	2.6
1975	1	1.2	0.8			1.1	0.8				2.1a	0.7	2.9	0.3			1.7
	2	0.6a	0.8				0.7				1.7	0.7	2.3	0.3		1.2	1.2
	3	1.0a	1.0				1.2				2.1	0.6	3.0	0.4		1.9	1.7
	4	0.9a	1.1				1.2				2.4	1.1	2.9	0.5	0.3	3.2	2.2

TABLE 7-3. (continued)

Station	Type	Boston MA 1	New York NY 1	Phila. PA 1	Phila. PA 4	Wash. DC 1	Detroit MI 1	Chicago IL 1	Chicago IL 2	Chicago IL 3	Houston TX 1	Houston TX 4	Dallas/Ft. Worth TX 1	Dallas/Ft. Worth TX 2	Dallas/Ft. Worth TX 1	Los Angeles CA 1	Los Angeles CA 2
Year	Quarter																
1976	1										0.8a	0.5	0.7a	0.3	0.2		
	2					1.2a					0.7a	0.5	0.7	0.3	0.4		
	3					1.4					1.1	0.7	1.1a	0.3	0.3		
	4					0.4a										4.1	3.0
1977	1			1.3	1.0	1.2	1.1						2.3			3.3	2.4
	2			1.6	0.8		0.9				0.3a	0.2	1.2	0.2	0.2	1.7	1.4
	3	0.6a		1.4	0.9	0.9a	1.0				0.8	0.3	1.1	0.2	0.2	1.8	1.6
	4	0.7		1.3	1.0	2.1					1.3	0.7	1.6a	0.5	0.5	3.8	2.9
1978	1	0.8		1.2	0.8	2.2					1.0	0.5	1.7a	0.4	0.3	2.2a	1.6
	2	1.0a		1.1	0.7	1.1					0.8	0.4	1.1	0.4	0.3		
	3	0.9		1.4	0.7	1.1					0.8	0.5	1.3	0.4	0.3	1.6	
	4	1.3	1.3	1.6	1.2	3.3					1.7	0.9	1.7	0.5	0.6	1.9	
1979	1	1.0	1.0a	1.1	0.7	1.8					0.9	0.4	1.2a	0.4	0.4	1.5	
	2	0.4	0.9	1.2	0.6	1.3		0.7	0.9	0.8	0.8	0.4	0.6a	0.2	0.3	0.9	
	3	0.6		1.0	0.6	1.6		0.5	0.6	0.8	0.5a	0.6a	1.1a	0.4	0.5	1.0a	
	4	0.8a		1.2	0.8	1.9					0.7a	0.5	0.5a	0.3	0.4	0.6a	
1980	1	0.9a		0.7	0.4		0.3	0.4	0.3	0.3	0.6a	0.3	0.3a	0.3	0.2	0.7	1.1
	2			0.4	0.4		0.3	0.7	0.4	0.6	0.3a	0.3a	0.6a	0.1	0.2		0.8
	3	0.5		0.7	0.4		0.3	1.0	0.5	0.5		0.2	0.3	0.1	0.1	1.1a	1.0
	4	0.6		0.7	0.5		0.4a	0.5	0.4	0.4		0.4	0.4	0.3	0.3		1.7
1981	1	0.4		0.5	0.4a		0.3	0.2	0.3	0.2	0.7	0.5	0.6	0.3	0.3	1.3	1.0
	2	0.3		0.4	0.3		0.3	0.4	0.3	0.3	0.2	0.2	0.3	0.1	0.2	0.7	0.7
	3			0.4	0.2		0.3	0.3	0.3	0.2	0.5	0.3		0.2	0.3	0.8	0.8
	4			0.4	0.3		0.3a	0.4	0.2a	0.3	0.8	1.0a		0.3	0.4	1.3	1.1
1982	1				0.3			0.4	0.3	0.3						0.8	0.7
	2		0.5		0.3			0.2	0.4	0.3						0.5	
	3	1.0	0.5		0.3			0.3	0.3	0.2						0.8	
	4		0.8a		0.4			0.4	0.3	0.3						1.1	0.6

Station type: 1. center city commercial
2. center city residential
3. center city industrial
4. suburban residential

a: less than required number of 24-hour sampling periods to meet composite criteria

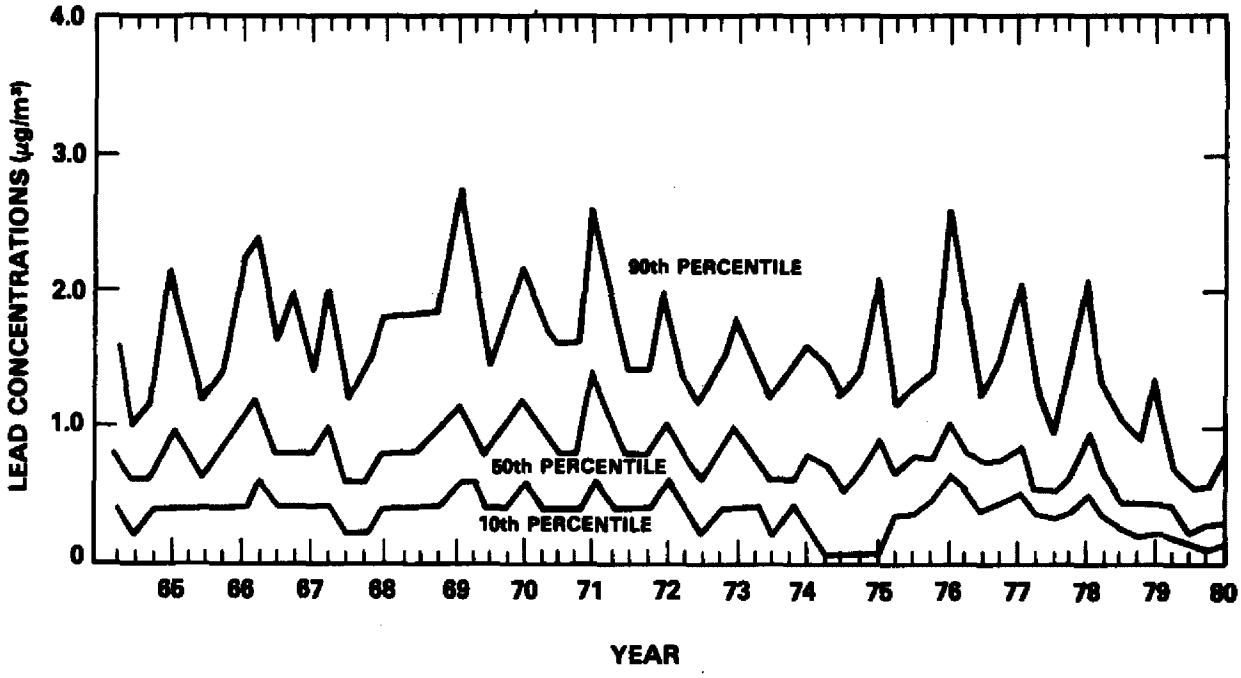

Figure 7-3. Seasonal patterns and trends in quarterly average urban lead concentrations.

7.2.1.1.2 Global distributions of air lead. Other industrialized nations have maintained networks for monitoring atmospheric lead. For example, Kretzschmar et al. (1980) reported trends from 1972 to 1977 in a 15-station network in Belgium. Annual averages ranged from 0.16 $\mu g/m^3$ at rural sites to 1.2 $\mu g/m^3$ near the center of Antwerp. All urban areas showed a maximum near the center of the city, with lead concentrations decreasing outward. The rural background levels appeared to range from 0.1 to 0.3 $\mu g/m^3$. Representative data from other nations appear in Table 7-1.

7.2.1.1.3 Natural concentrations of lead in air. There are no direct measurements of prehistoric natural concentrations of lead in air. Air lead concentrations which existed in prehistoric times must be inferred from available data. Table 7-1 lists several values for remote areas of the world, the lowest of which is 0.000076 $\mu g/m^3$ at the South Pole (Maenhaut et al., 1979). Two other reports show comparable values: 0.00017 $\mu g/m^3$ at Eniwetok in the Pacific Ocean (Settle and Patterson, 1982) and 0.00015 at Dye 3 in Greenland (Davidson et al., 1981a). Since each of these studies reported some anthropogenic influence, it may be assumed that natural lead concentrations are somewhat lower than these measured values.

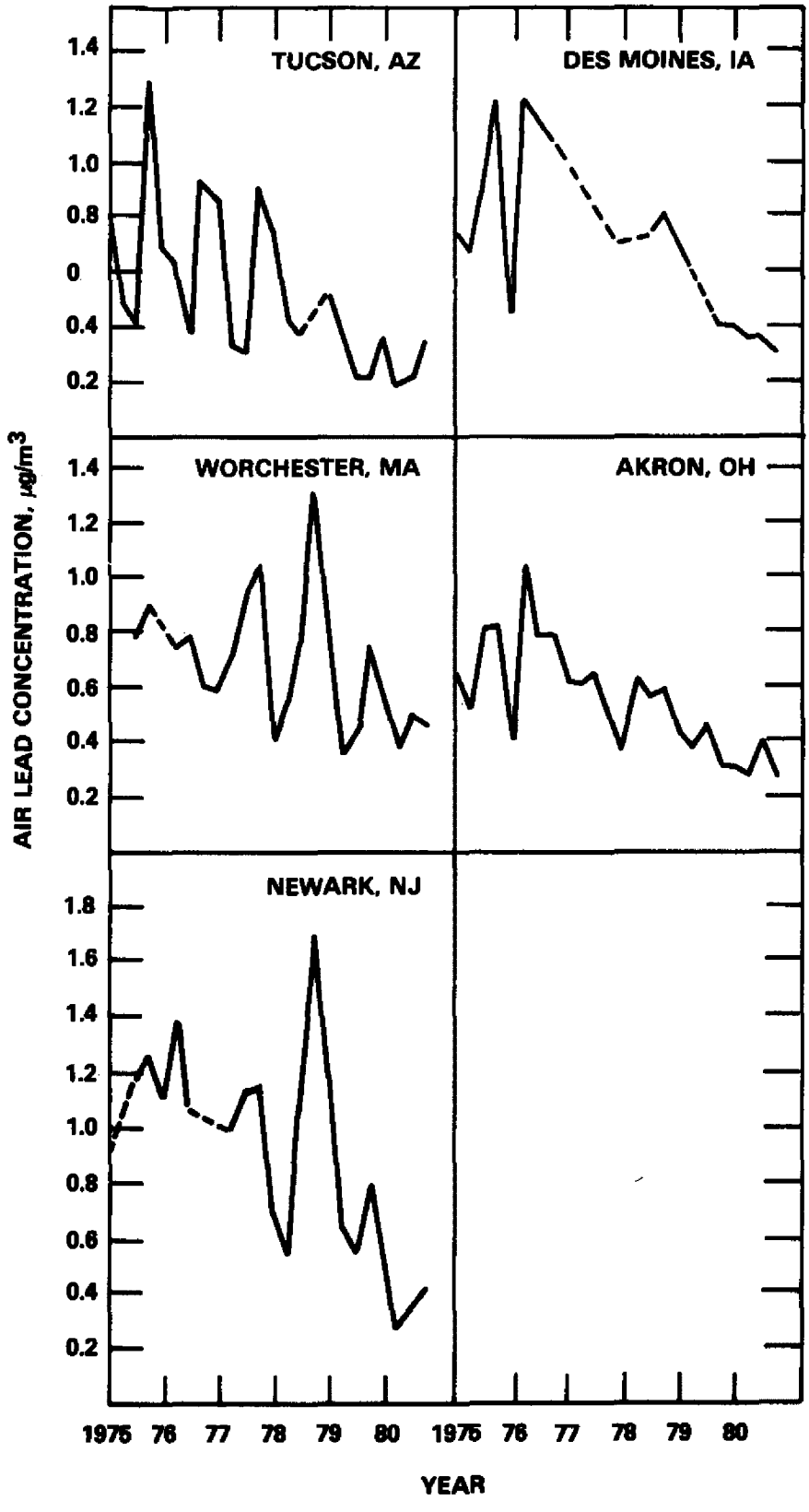

Figure 7-4. Time trends in ambient air lead at selected urban sites.

Another approach to determining natural concentrations is to estimate global emissions from natural sources. Nriagu (1979) estimated emissions at 24.5 x 10^6 kg/yr, whereas Settle and Patterson (1980) estimated a lower value of 2 x 10^6 kg/yr. An average troposheric volume, to which surface generated particles are generally confined, is about 2.55 x $10^{10}m^3$. Assuming a residence time of 10 days (see Section 6.3), natural lead emissions during this time would be 6.7 x 10^{14} µg. The air concentrations would be 0.000263 using the values of Nriagu (1979) or 0.0000214 µg/m^3 using the data of Settle and Patterson (1980). It seems likely that the concentration of natural lead in the atmosphere is between 0.00002 and 0.00007 µg/m^3. A value of 0.00005 µg/m^3 will be used for calculations regarding the contribution of natural air lead to total human uptake in Section 7.3.1.

7.2.1.2 Compliance with the 1978 Air Quality Standard. Table 7-4 lists stations operated by state and local agencies where one or more quarterly averages exceeded 1.0 µg/m^3 or the current standard of 1.5 µg/m^3 in 1979 or 1980. A portion of each agency's compliance monitoring network consists of monitors sited in areas expected to yield high concentrations associated with identifiable sources. In the case of lead, these locations are most likely to be near stationary point sources such as smelters or refineries, and near routes of high traffic density. Both situations are represented in Table 7-4; e.g., the Idaho data reflect predominantly stationary source emissions, whereas the Washington, D.C. data reflect predominantly vehicular emissions.

Table 7-5 summarizes the maximum quarter lead values for those stations reporting 4 valid quarters in 1979, 1980, and 1981, grouped according to principal exposure orientation or influence--population, stationary source, or background. The sites located near stationary sources clearly dominate the concentrations over 2.0 µg/m^3; however, new siting guidelines, discussed in Section 7.2.1.3.2, will probably effect some increase in the upper end of the distribution of values from population-oriented sites by adding sites closer to traffic emissions.

The effect of the 1978 National Ambient Air Quality Standard for Lead has been to reduce the air concentration of lead in major urban areas. Similar trends may also be seen in urban areas of lower population density (Figure 7-4). Continuous monitoring at non-urban stations has been insufficient to show a trend at more than a few locations.

7.2.1.3 Changes in Air Lead Prior to Human Uptake. There are many factors which can cause differences between the concentration of lead measured at a monitoring station and the actual inhalation of air by humans. The following sections show that air lead concentrations usually decrease with vertical and horizontal distance from emission sources, and are generally lower indoors than outdoors. A person working on the fifth floor of an office building would be exposed to less lead than a person standing on a curb at street level. The following discussions will describe how these differences can affect individual exposures in particular circumstances.

TABLE 7-4. STATIONS WITH AIR LEAD CONCENTRATIONS GREATER THAN 1.0 μg/m³

Data are listed from all stations, urban and rural, reporting valid quarterly averages greater than 1.0 μg/m³. Some stations have not yet reported data for 1981.

	Station #	1979 No. of Quarters >1.0	>1.5	Max Qtrly Ave	1980 No. of Quarters >1.0	>1.5	Max Qtrly Ave	1981 No of Quarters >1.0	>1.5	Max Qtrly Ave
Troy, AL	(003)	2	2	2.78	2	0	1.13	2	2	4.32
Glendale, AZ	(001)	1	0	1.06						
Phoenix, AZ	(002A)	1	1	1.54	2	0	1.29	1	0	1.17
" "	(002G)	2		2.59	2	0	1.49	2	0	1.39
" "	(004)	2	0	1.48				1	0	1.04
" "	(013)	2		1.55	1	0	1.06			
Scottsdale, AZ	(003)	2	0	1.41	1	0	1.13	1	0	1.08
Tucson, AZ	(009)	1	0	1.18						
Nogales, AZ	(004)				1	0	1.10			
Los Angeles, CA	(001)	1	1	1.51				2	0	1.43
Anaheim, CA	(001)	1	0	1.11						
Adams Co, CO	(001)	2	1	1.77						
Arapahoe Co, CO	(001)	1	0	1.10						
Arvada, CO	(001)	1	1	1.60						
Brighton, CO	(001)	1	0	1.17						
Colorado Springs, CO	(004)	1	0	1.37						
Denver, CO	(001)	2	1	1.70						
" "	(002)	4	3	3.47	2	1	1.53			
" "	(003)	3	1	2.13	1	0	1.03			
" "	(009)	1	1	1.57	2	0	1.23			
" "	(010)	2	1	1.67						
" "	(012)	2	1	1.67	1	0	1.10			
Englewood, CO	(001)	1	1	1.80						
Garfield, CO	(001)	1	0	1.20						
Grand Junction, CO	(010)	2	1	1.53	1	0	1.27			
Longmont, CO	(001)	2	0	1.07						
Pueblo, CO	(001)	1	0	1.03						
" "	(003)	1	0	1.03						
Routt Co, CO	(003)	1	0	1.33						
New Haven, CT	(123)	3		1.57						
Waterbury, CT	(123)	2	0	1.41						
Wilmington, DE	(002)	2	0	1.21						

TABLE 7-4. (continued)

	Station #	1979 No. of Quarters >1.0	1979 No. of Quarters >1.5	Max Qtrly Ave	1980 No. of Quarters >1.0	1980 No. of Quarters >1.5	Max Qtrly Ave	1981 No of Quarters >1.0	1981 No of Quarters >1.5	Max Qtrly Ave
Washington, DC	(005)	1	0	1.49						
" "	(007)	4		1.89						
" "	(008)	1	1	1.90						
" "	(011)	2	0	1.44						
" "	(015)	2	0	1.06						
" "	(017)	1	0	1.45						
Dade Co, FL	(020)	1	0	1.16						
Miami, FL	(016)	3	0	1.46	2	0	1.10			
Perrine, FL	(002)	1	0	1.01						
Hillsborough, FL	(082)	2	0	1.31	1	0	1.09			
Tampa, FL	(043)	3		1.60	1	0	1.07			
Boise, ID	(003)				1	0	1.01			
Kellogg, ID	(004)	4		9.02	2		6.88			
" "	(006)	4	4	8.25	4	4	8.72	4	4	6.67
Shoshone Co, ID	(015)	2	0	1.21						
" "	(016)	1	1	2.27	1	0	1.02			
" "	(017)	4		4.57	3		3.33	2	2	1.54
" "	(020)	2		4.11	2		2.15	1	0	1.49
" "	(021)	4	4	13.54	4	4	13.67	4	4	11.82
" "	(027)	4		10.81	3		7.18			
Chicago, IL	(022)				1	0	1.02			
" "	(030)				1	0	1.06			
" "	(005)	1	0	1.05						
" "	(036)	1	0	1.02						
" "	(037)	1	0	1.14						
Cicero, IL	(001)	1	0	1.00						
Elgin, IL	(004)				1	1	1.95			
Granite City, IL	(007)	1	0	1.04						
" "	(009)	4	0	1.15						
" "	(010)	4	4	3.17	3	2	2.97	4	3	7.27
" "	(011)	4	0	1.33	1	0	1.43	1	0	1.13
Jeffersonville, IN	(001)	3	0	1.38						
East Chicago, IL	(001)	2		2.19						
" "	(003)	2	0	1.42						
" "	(004)	1	1	1.67						
" "	(006)	2	0	1.34	1	0	1.04			

TABLE 7-4. (continued)

	Station #	1979 No. of Quarters >1.0	>1.5	Max Qtrly Ave	1980 No. of Quarters >1.0	>1.5	Max Qtrly Ave	1981 No of Quarters >1.0	>1.5	Max Qtrly Ave
Hammond, IN	(004)	2	0	1.18						
" "	(006)	1	0	1.46						
Indianapolis, IN	(030)	1	0	1.16						
Des Moines, IA	(051)	1	0	1.30						
Buechel, KY	(001)				1	0	1.41			
Covington, KY	(001)	2	0	1.12						
" "	(008)	1	0	1.16						
Greenup Co, KY	(003)	1	0	1.42						
Jefferson Co, Ky	(029)	1	0	1.05	1	1	1.78			
Louisville, KY	(004)	1	0	1.01	1	1	2.41			
" "	(009)				1	1	1.75			
" "	(019)				1	1	1.59			
" "	(020)				1	1	2.52			
" "	(021)	1	0	1.29	1	1	1.42			
" "	(028)	1	0	1.06						
Newport, KY	(002)	1	0	1.06						
Okolona, KY	(001)	1	1	1.51	2	1	2.31			
Paducha, KY	(004)	1	0	1.41						
" "	(020)	1	0	1.22						
St. Matthews, KY	(004)	1	0	1.20	1	1	1.83			
Shively, KY	(002)	1	1	1.56						
Baton Rouge, LA	(002)	1	1	1.57						
Portland, ME	(009)	2	0	1.02						
Anne Arundel Co, MD	(001)	1	0	1.27						
" "	(003)	2	0	1.45						
Baltimore, MD	(001)	2	0	1.06						
" "	(006)	1	0	1.09						
" "	(008)	1	0	1.24						
" "	(009)	1	0	1.08						
" "	(018)	2	0	1.12						
Cheverly, MD	(004)	4	1	1.51						
Essex, MD	(001)	2	0	1.15						
Hyattsville, MD	(001)	2	0	1.18						
Springfield, MA	(002)	1	1	1.68	1	0	1.04			
Boston, MA	(012)	1	0	1.01						

TABLE 7-4. (continued)

	Station #	1979 No. of Quarters >1.0	1979 No. of Quarters >1.5	1979 Max Qtrly Ave	1980 No. of Quarters >1.0	1980 No. of Quarters >1.5	1980 Max Qtrly Ave	1981 No of Quarters >1.0	1981 No of Quarters >1.5	1981 Max Qtrly Ave
Minneapolis, MN	(027)	1	1	2.44						
" "	(055)				3		2.41	3	1	1.52
Richfield, MN	(004)	4		1.95	2	0	1.18			
St. Louis Park, MN	(007)	2		2.87	4		3.04			
St. Paul, MN	(031)	1	0	1.04						
" "	(038	1	0	1.36	3		1.82	2	2	3.11
Lewis & Clark Co, MT	(002)	4		4.19	4		2.75	2	2	3.19
" "	(008)				1	0	1.19			
Omaha, NE	(034)	1	0	1.08						
Las Vegas, NV	(001)	1	0	1.15						
Newark, NJ	(001)	1	0	1.17						
Perth Amboy, NJ	(001)	1	0	1.08						
Paterson, NJ	(001)	1	0	1.42						
Elizabeth, NJ	(002)	1	0	1.16						
Yonkers, NY	(001)	1	0	1.08						
Cincinnatti, OH	(001)	1	0	1.15						
Laureldale, PA	(717)	4		3.30	2		1.86	4	3	2.18
Reading, PA	(712)	1	0	1.11						
E.Conemaugh, PA	(804)	3	0	1.28						
Throop, PA	(019)	3	0	1.13						
Lancaster City, PA	(315)	1	0	1.18						
New Castle, PA	(015)	1	0	1.01						
Montgomery Co, PA	(103)	1	0	1.23						
Pottstown, PA	(101)	1	0	1.16						
Phila., PA	(026)	3	0	1.21						
" "	(028)	4		2.71	3	0	1.26	1	0	1.30
" "	(031)	2	0	1.29						
" "	(038)	1	0	1.06						
Guaynabo Co, PR	(001)	2		1.60	1	0	1.06	1	0	1.02
Ponce, PR	(002)	1	0	1.08						
San Juan Co., PR	(003)	4		3.59						
E.Providence, RI	(008)	2	0	1.10						
Providence, RI	(007)	4		1.92	2	0	1.16			
" "	(015)	1	0	1.34						
Greenville, SC	(001)	2	0	1.38						

TABLE 7-4. (continued)

	Station #	1979 No. of Quarters >1.0	>1.5	Max Qtrly Ave	1980 No. of Quarters >1.0	>1.5	Max Qtrly Ave	1981 No of Quarters >1.0	>1.5	Max Qtrly Ave
Nashville/Davidson, TN	(006)	1	0	1.05						
San Antonio, TX	(034)	1	0	1.23						
Dallas, TX	(018)	1	1	1.59						
" "	(029)	1	0	1.07						
" "	(035)	1	0	1.12						
" "	(046)	1	0	1.22						
" "	(049)	1	0	1.01						
" "	(050)	2	0	1.13						
El Paso, TX	(002A)	1	1	1.90			2.12			
" "	(002F)	1	1	1.90				4	1	1.79
" "	(002G)	4		2.60						
" "	(018)	2		1.91						
" "	(021)	1	0	1.02						
" "	(022)	2		1.84						
" "	(023)	2		2.12						
" "	(027)	2		2.15	2		1.74	4	2	1.75
" "	(028)				1	0	1.16			
" "	(030)	1	0	1.02						
" "	(031)	1	1	2.47						
" "	(033)	1	1	1.97						
Houston, TX	(001)	2	0	1.35						
" "	(002)	2	0	1.39						
" "	(037)	1	0	1.26						
" "	(049)	3	0	1.13				1	1	1.96
Ft. Worth, TX	(003)	2	0	1.14						
Seattle, WA	(057)	1	0	1.36						
Tacoma, WA	(004)	1	0	1.06						
Charleston, WV	(001)	1	0	1.09						

TABLE 7-5. DISTRIBUTION OF AIR LEAD CONCENTRATIONS BY TYPE OF SITE

Site-type	Concentration ranges ($\mu g/m^3$) ≤.5	>.5 ≤1.0	>1.0 ≤1.5	>1.5 ≤2.0	>2.0	Total no.of site-years
Population	300	173	46	7	5	531
Stationary source	50	12	10	2	21	95
Background	21	0	0	0	0	21
Total (site-years)	371	185	56	9	26	647
Percent of sites in concentration range	57%	29%	9%	1%	4%	100%

Data are the number of site years during 1979-81 falling within the designated quarterly average concentration range. To be included, a site year must have four valid quarters of data.

7.2.1.3.1 Airborne particle size distributions. The effects of airborne lead on human health and welfare depend upon the sizes of the lead-containing particles. As discussed in Chapter 6, large particles are removed relatively quickly from the atmosphere by dry and wet deposition processes. Particles with diameter smaller than a few micrometers tend to remain airborne for long periods (see Section 6.3.1).

Figure 7-5 summarizes airborne lead particle size data from the literature. Minimum and maximum aerodynamic particle diameters of 0.05 μm and 25 μm, respectively, have been assumed unless otherwise specified in the original reference. Note that most of the airborne lead mass is associated with small particles. There is also a distinct peak in the upper end of many of the distributions. Two separate categories of sources are responsible for these distributions: the small particles result from nucleation of vapor phase lead emissions (predominantly automotive), while the larger particles represent primary aerosol emitted from combustion or from mechanical processes (such as soil erosion, abrasion of metal products, resuspension of automobile tailpipe deposits, and flaking of paint).

Information associated with each in the distributions in Figure 7-5 may be found in Table 7A-1 of Appendix 7A. The first six distributions were obtained by an EPA cascade impactor network established in several cities during the calendar year 1970 (Lee et al., 1972). These

distributions represent the most extensive size distribution data base available. However, the impactors were operated at excessive air flow rates that most likely resulted in particle bounceoff, biasing the data toward smaller particles (Dzubay et al., 1976). Many of the later distributions, although obtained by independent investigators with unknown quality control, were collected using techniques which minimize particle bounceoff and hence may be more reliable. It is important to note that a few of the distributions were obtained without backup filters that capture the smallest particles. These distributions are likely to be inaccurate, since an appreciable fraction of the airborne lead mass was probably not sampled. The distributions of Figure 7-5 have been used with published lung deposition data to estimate the fraction of inhaled airborne lead deposited in the human respiratory system (see Chapter 10).

7.2.1.3.2 Vertical gradients and siting guidelines. New guidelines for placing ambient air lead monitors went into effect in July, 1981 (F.R., 1981). "Microscale" sites, placed between 5 and 15 meters from thoroughfares and 2 to 7 meters above the ground, are prescribed, but until now few monitors have been located that close to heavily traveled roadways. Many of these microscale sites might be expected to show higher lead concentrations than that measured at nearby middlescale urban sites, due to vertical gradients in lead concentrations near the source. One study (PEDCo, 1981) gives limited insight into the relationship between a microscale location and locations further from a roadway. The data in Table 7-6 summarize total suspended particulates and particulate lead concentrations in samples collected in Cincinnati, Ohio, on 21 consecutive days in April and May, 1980, adjacent to a 58,500 vehicles-per-day expressway connector. Simple interpolation indicates that a microscale monitor as close as 5 meters from the roadway and 2 meters above the ground would record concentrations some 20 percent higher than those at a "middle scale" site 21.4 meters from the roadway. On the other hand, these data also indicate that although lead concentrations very close to the roadway (2.8 m setback) are quite dependent on the height of the sampler, the averages at the three selected heights converge rapidly with increasing distance from the roadway. In fact, the average lead concentration (1.07 $\mu g/m^3$) for the one monitor (6.3 m height, 7.1 m setback) that satisfies the microscale site definition proves not to be significantly different from the averages for its two companions at 7.1 m, or from the averages for any of the three monitors at the 21.4 m setback. It also appears that distance from the source, whether vertical or horizontal, can be the primary determining factor for changes in air lead concentrations. At 7.1 m from the highway, the 1.1 and 6.3 m samplers would be about 7 and 11 meters from the road surface. The values at these vertical distances are only slightly lower than the corresponding values for comparable horizontal distances.

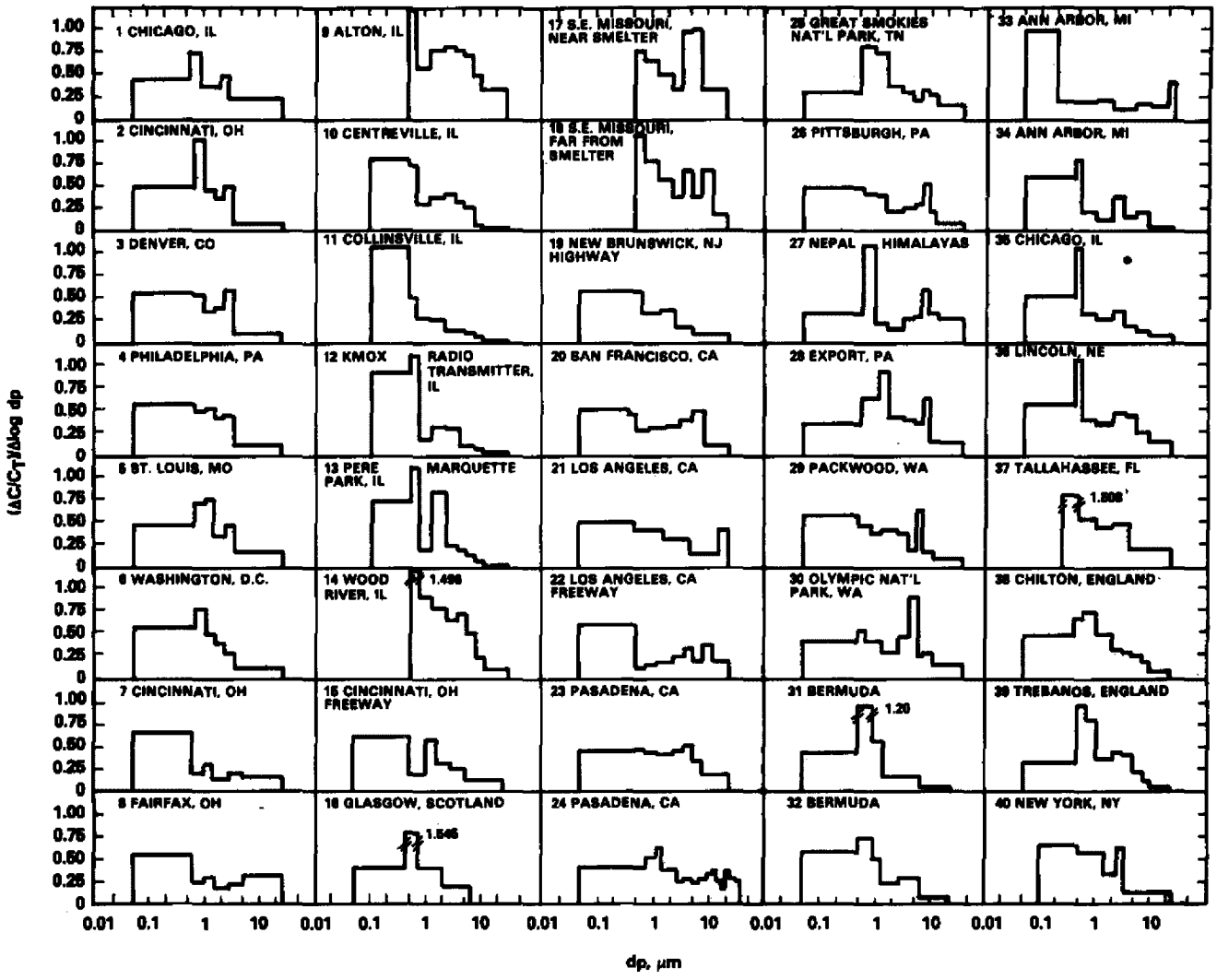

Figure 7-5. Airborne mass size distributions for lead taken from the literature. ΔC represents the airborne lead concentration in each size range, C_T is the total airborne lead concentration in all size ranges, and d_p is the aerodynamic particle diameter. A density of 6 g/cm³ for lead-containing particles has been used to convert aerodynamic to physical diameter when applying the lower end of the lung deposition curves of Figures 7-3 through 7-5.

TABLE 7-6. VERTICAL DISTRIBUTION OF LEAD CONCENTRATIONS

	Setback distance (m)	Height (m)	Effective[1] distance from source (m)	Air lead conc. ($\mu g/m^3$)	Ratio to source
Kansas City east of road	3.0*	6.1	6.4	1.7	0.85
		1.5	3.2	2.0	S
Kansas City west of road	3.0*	6.1	6.4	1.5	0.88
		1.5	3.2	1.7	S
Cincinnati east of road	3.0*	6.1	6.4	0.9	0.64
		1.5	3.2	1.4	S
Cincinnati west of road	3.0*	6.1	6.4	0.6	0.75
		1.5	3.2	0.8	S
Cincinnati	2.8	10.5	10.4	0.81	0.61
		6.3	6.4	0.96	0.72
		1.1	2.9	1.33	S
Cincinnati	7.1	10.5	12.3	0.93	0.69
		6.3	9.2	1.07	0.80
		1.1	7.1	1.16	0.87
Cincinnati	21.4	10.5	23.6	0.90	0.68
		6.3	22.2	0.97	0.73
		1.1	21.4	1.01	0.77

S = Station closest to source used to calculate ratio.

[1]Effective distance was calculated assuming the source was the edge of the roadway at a height of 0.1 m.

*Assumed setback distance of 3.0 m.

Other urban locations around the country with their own characteristic wind flow patterns and complex settings, such as multiple roadways, may produce situations where the microscale site does not record the highest concentrations. Collectively, however, the addition of these microscale sites to the nation's networks can be expected to shift the distribution of reported quarterly averages toward higher values. This shift will result from the change in composition of the networks and is a separate phenomenon from downward trend at long established sites described above, reflecting the decrease in lead additives used in gasoline.

Two other studies show that lead concentrations decrease with vertical distance from the source. PEDCo-Environmental (1977) measured lead concentrations at heights of 1.5 and 6.1 m at sites in Kansas City, MO and Cincinnati, OH. The sampling sites in Kansas City were described as unsheltered, unbiased by local pollution influences, and not immediately surrounded by large buildings. The Cincinnati study was conducted in a primarily residential area with one commercial street. Samplers were operated for 24-hour periods; however, a few 12-hour samples were collected from 8 AM to 8 PM. Data were obtained in Kansas City on 35 days and in Cincinnati on 33 days. The range and average values reported are shown in Table 7-7. In all cases except two, the measured concentrations were greater at 1.5 meters than at 6.1 meters. Note that the difference between the east side and west side of the street was approximately the same as the difference between 1.5 m and 6.1 m in height.

Sinn (1980) investigated airborne lead concentrations at heights of 3 and 20 m above a road in Frankfurt, Germany. Measurements conducted in December 1975, December 1976, and January 1978 gave monthly mean values of 3.18, 1.04, and 0.66 $\mu g/m^3$, respectively, at 3 m. The corresponding values at 20 m were 0.59, 0.38, and 0.31 $\mu g/m^3$, showing a substantial reduction at this height. The decrease in concentration over the 2-year period was attributed to a decrease in the permissible lead content of gasoline from 0.4 to 0.15 g/liter beginning in January 1976.

Two reports show no relationship between air concentration and vertical distance. From August 1975 to July 1976, Barltrop and Strehlow (1976) conducted an air sampling program in London at a proposed nursery site under an elevated motorway. The height of the motorway was 9.3 m. Air samplers were operated at five to seven sites during the period from Monday to Friday, 8 AM to 6 PM, for one year. The maximum individual value observed was 18 $\mu g/m^3$. The 12 month mean ranged from 1.35 $\mu g/m^3$ to 1.51 $\mu g/m^3$, with standard deviations of 0.91 and 0.66, respectively. The authors reported that the airborne concentrations were independent of height from ground level up to 7 m.

Ter Haar (1979) measured airborne lead at several heights above the ground, using samplers positioned 6 m from a heavily traveled road in Detroit. A total of nine 8-hour daytime samples were collected. The overall average airborne lead concentrations at heights of 0.3, 0.9, 1.5, and 3.0 m were 4.2, 4.8, 4.7, and 4.6 $\mu g/m^3$, respectively, indicating a uniform concentration over this range of heights at the measurement site. It should be noted that at any one height, the concentration varied by as much as a factor of 10 from one day to the next; the importance of simultaneous sampling when attempting to measure gradients is clearly demonstrated.

Data that show variations with vertical distance reflect the strong influence of the geometry of the boundary layer, wind, and atmospheric stability conditions on the vertical gradient of lead resulting from automobile emissions. The variability of concentration with height

is further complicated by the higher emission elevation of smokestacks. Concentrations measured from sampling stations on the roofs of buildings several stories high may not reflect actual human exposure conditions, but neither would a single sampling station located at ground level in a building complex. The height variation in concentration resulting from vertical diffusion of automobile emissions is likely to be small compared to temporal and spatial variations resulting from surface geometry, wind, and atmospheric conditions. Our understanding of the complex factors affecting the vertical distribution of airborne lead is extremely limited, but the data of Table 7-6 indicate that air lead concentrations are primarily a function of distance from the source, whether vertical or horizontal.

7.2.1.3.3 Indoor/outdoor relationships. Because people spend much of their time indoors, ambient air data may not accurately indicate actual exposure to airborne lead. Table 7-7 summarizes the results of several indoor/outdoor airborne lead studies. In nearly all cases, the indoor concentration is substantially lower than the corresponding value outdoors; the only indoor/outdoor ratio exceeding unity is for a high-rise apartment building, where air taken in near street level is rapidly distributed through the building air circulation system. Some of the studies in Table 7-7 show smaller indoor/outdoor ratios during the winter, when windows and doors are tightly closed. Overall, the data suggest indoor/outdoor ratios of 0.6 to 0.8 are typical for airborne lead in houses without air conditioning. Ratios in air conditioned houses are expected to be in the range of 0.3 to 0.5 (Yocum, 1982).

The available data imply that virtually all airborne lead found indoors is associated with material transported from the outside. Because of the complexity of factors affecting infiltration of air into buildings, however, it is difficult to predict accurately indoor lead concentrations based on outdoor levels. Even detailed knowledge of indoor and outdoor airborne lead concentrations at fixed locations may still be insufficient to assess human exposure to airborne lead. The study of Tosteson et al. (1982) in Table 7-7 included measurement of airborne lead concentrations using personal exposure monitors carried by individuals going about their day-to-day activities. In contrast to the lead concentrations of 0.092 and 0.12 $\mu g/m^3$ at fixed locations, the average personal exposure was 0.16 $\mu g/m^3$. The authors suggest this indicates an inadequacy of using fixed monitors at either indoor or outdoor locations to assess exposure.

7.2.2 Lead in Soil

Much of the lead in the atmosphere is transferred to terrestrial surfaces where it is eventually passed to the upper layer of the soil surface. The mechanisms which determine the transfer rate of lead to soil are described in Section 6.4.1 and the transformation of lead in

profile. It is assumed that particles deposited directly on the roadway are washed to the edge of the pavement, but do not migrate beyond the shoulder.

Near primary and secondary smelters, lead in soil decreases exponentially within a 5 to 10 km zone around the smelter complex. Soil lead contamination varies with the smelter emission rate, length of time the smelter has been in operation, prevailing windspeed and direction, regional climatic conditions, and local topography (Roberts, 1975).

Little and Martin (1972) observed decreases from 125 to 10 µg/g in a 6 km zone around a smelting complex in Great Britain; all of the excess lead was in the upper 6 cm of the soil profile. Roberts (1975) reported soil lead between 15,000 and 20,000 µg/g near a smelter in Toronto. Kerin (1975) found 5,000 to 9,000 µg/g adjacent to a Yugoslavian smelter; the contamination zone was 7 km in radius. Ragaini et al. (1977) observed 7900 µg/g near a smelter in Kellogg, Idaho; they also observed a 100-fold decrease at a depth of 20 cm in the soil profile. Palmer and Kucera (1980) observed soil lead in excess of 60,000 µg/g near two smelters in Missouri, decreasing to 10 µg/g at 10 km.

Urban soils may be contaminated from a variety of atmospheric and non-atmospheric sources. The major sources of soil lead seem to be paint chips from older houses and deposition from nearby highways. Lead in soil adjacent to a house decreases with distance from the house; this may be due to paint chips or to dust of atmospheric origin washing from the rooftop (Wheeler and Rolfe, 1979).

Andresen et al. (1980) reported lead in the litter layer of 51 forest soils in the northeastern United States. They found values from 20 to 700 µg/g, which can be compared only qualitatively to the soil lead concentration cited above. This study clearly shows that the major pathway of lead to the soil is by the decomposition of plant material containing high concentrations of atmospheric lead on their surface. Because this organic matter is a part of the decomposer food chain, and because the organic matter is in dynamic equilibrium with soil moisture, it is reasonable to assume that lead associated with organic matter is more mobile than lead tightly bound within the crystalline structure of inorganic rock fragments. This argument is expressed more precisely in the discussions below.

Finally, a definitive study which describes the source of soil lead was reported by Gulson et al. (1981) for soils in the vicinity of Adelaide, South Australia. In an urban to rural transect, stable lead isotopes were measured in the top 10 cm of soils over a 50 km distance. By their isotopic compositions, three sources of lead were identified: natural, non-automotive industrial lead from Australia, and tetraethyl lead manufactured in the United States. The results indicated that most of the soil surface lead originated from leaded gasoline. Similar studies have not been conducted in the United States.

soil in Section 6.5.1. The uptake of lead by plants and its subsequent effect on animals may be found in Section 8.2. The purpose of this section is to discuss the distribution of lead in U.S. soils and the impact of this lead on potential human exposures.

7.2.2.1. Typical Concentrations of Lead in Soil.

7.2.2.1.1 Lead in urban, smelter, and rural soils. Shacklette et al. (1971) sampled soils at a depth of 20 cm to determine the elemental composition of soil materials derived from the earth's crust, not the atmosphere. The range of values probably represent natural levels of lead in soil, although there may have been some contamination with anthropogenic lead during collection and handling. Lead concentrations in soil ranged from less than 10 to greater than 70 μg/g. The arithmetic mean of 20 and geometric mean of 16 μg/g reflect the fact that most of the 863 samples were below 30 μg/g at this depth. McKeague and Wolynetz (1980) found the same arithmetic mean (20 μg/g) for 53 uncultivated Canadian soils. The range was 5 to 50 μg/g and there was no differences with depth between the A, B and C horizons in the soil profile.

Studies discussed in Section 6.5.1 have determined that atmospheric lead is retained in the upper two centimeters of undisturbed soil, especially soils with at least 5 percent organic matter and a pH of 5 or above. There has been no general survey of this upper 2 cm of the soil surface in the United States, but several studies of lead in soil near roadsides and smelters and a few studies of lead in soil near old houses with lead-based paint can provide the backgound information for determining potential human exposures to lead from soil.

Because lead is immobilized by the organic component of soil (Section 6.5.1), the concentration of anthropogenic lead in the upper 2 cm is determined by the flux of atmospheric lead to the soil surface. Near roadsides, this flux is largely by dry deposition and the rate depends on particle size and concentration. These factors vary with traffic density and average vehicle speed (see Section 6.4.1). In general, deposition flux drops off abruptly with increasing distance from the roadway. This effect is demonstrated in studies which show that surface soil lead decreases exponentially up to 25 m from the edge of the road. The original work of Quarles et al. (1974) showed decreases in soil lead from 550 to 40 μg/g within 25 m alongside a highway with 12,500 vehicles/day in Virginia. Their findings were confirmed by Wheeler and Rolfe (1979), who observed an exponential decrease linearly correlated with traffic volume. Agrawal et al (1981) found similar correlations between traffic density and roadside proximity in Baroda City, as did Garcia-Miragaya et al. (1981) in Venzuela and Wong and Tam (1978) in Hong Kong. The extensive study of Little and Wiffen (1978) is discussed in Chapter 6. These authors found additional relationships between particle size and roadside proximity and decreases with depth in the soil profile. The general conclusion from these studies is that roadside soils may contain atmospheric lead from 30 to 2000 μg/g in excess of natural levels within 25 meters of the roadbed, all of which is in the upper layer of the soil

off by rain nor taken up through the leaf surface. For many years, plant surfaces have been used as indicators of lead pollution (Garty and Fuchs, 1982; Pilegaard, 1978; Ratcliffe, 1975; Ruhling and Tyler, 1969; Tanaka and Ichikuni, 1982). These studies all show that lead on the surface of leaves and bark is proportional to traffic density and distance from the highway, or more specifically, to air lead concentrations and particle size distributions. Other factors such as surface roughness, wind direction and speed are discussed in Chapter 6. The data also show that lead in internal plant tissues is directly related to lead in soil.

In a study to determine the background concentrations of lead and other metals in agricultural crops, the Food and Drug Administration (Wolnik et al., 1983), in cooperation with the U.S. Department of Agriculture and the U.S. Environmental Protection Agency, analyzed over 1500 samples of the most common crops taken from a cross section of geographic locations. Collection sites were remote from mobile or stationary sources of lead. Soil lead concentrations were within the normal range (8-25 μg/g) of U.S. soils. Extreme care was taken to avoid contamination during collection, transportation, and analysis. The concentrations of lead in crops found by Wolnik et al. (1983) are shown as "Total" concentrations in Table 7-9. The breakdown by source of lead is discussed below. The total concentration data should probably be seen as representing the lowest concentrations of lead in food available to Americans. It is likely that lead concentrations in crops harvested by farmers are somewhat higher for several reasons: some crops are grown closer to highways and stationary sources of lead than those sampled by Wolnik et al. (1983); some harvest techniques used by farmers might add more lead to the crop than did Wolnik et al.; and some crops are grown on soils significantly higher in lead than those of the Wolnik et al. study because of a history of fertilizer additions or sludge applications.

Because the values reported by Wolnik et al. are of better quality than previously reported data for food crops, it is necessary to disregard many other reports as being either atypical or erroneous. Studies that specifically apply to roadside or stationary source conditions, however, may be applicable if the data are placed in the context of these recent findings by Wolnik et al. (1983). Studies of the lead associated with crops near highways have shown that both lead taken up from soil and aerosol lead delivered by deposition are found with the edible portions of common vegetable crops. However, there is enormous variability in the amount of lead associated with such crops and in the relative amounts of lead in the plants versus on the plants. The variability depends upon several factors, the most prominent of which are the plant species, the traffic density, the meteorological conditions, and the local soil conditions (Welch and Dick, 1975; Rabinowitz, 1974; Arvik, 1973; Dedolph et

7.2.2.1.2 Natural and anthropogenic sources of soil lead. Although no study has clearly identified the relative concentrations of natural and anthropogenic lead in soil, a few clarifying statements can be made with some certainty. Lead may be found in inorganic primary minerals, on humic substances, complexed with Fe-Mn oxide films, on secondary minerals or in soil moisture. All of the lead in primary minerals is natural and is bound tightly within the crystalline structure of the minerals. Most of this lead can be released only by harsh treatment with acids. The lead on the surface of these minerals is leached slowly into the soil moisture. Atmospheric lead forms complexes with humic substances or on oxide films that are in equilibrium with soil moisture, although the equilibrium strongly favors the complexing agents. Consequently, the ratio of anthropogenic to natural lead in soil moisture depends mostly on the amounts of each type of lead in the complexing agents and very little on the concentration of natural lead in the inorganic minerals.

Except near roadsides and smelters, only a few μg of atmospheric lead have been added to each gram of soil. Several studies indicate that this lead is available to plants (Section 8.3.1.1) and that even with small amounts of atmospheric lead, about 75 percent of the lead in soil moisture is of atmospheric origin. A conservative estimate of 50 percent is used in the discussions in Section 7.3.1.2. A breakdown of the types of lead in soil may be found in Table 7-8.

TABLE 7-8. SUMMARY OF SOIL LEAD CONCENTRATIONS†

Matrix	Natural lead	Atmospheric lead		Total lead	
		Rural	Urban	Rural	Urban
Total soil	8-25	3	50-150	10-30	150-300
Primary minerals	8-25	-	-	8-25	8-25
Humic substances*	20	60	2000	80	2000
Soil moisture	0.0005	0.0005	0.0150	0.001	0.0155

† All values in μg/g.
*Assumes 5% organic matter, pH 5.0; may also include lead in Fe-Mn oxide films.

Source: Section 6.5.1

7.2.2.2 Pathways of Soil Lead to Human Consumption.

7.2.2.2.1 Crops. Lead on the surfaces of vegetation may be of atmospheric origin, or a combination of atmospheric and soil in the internal tissues. As with soils, lead on vegetation surfaces decreases exponentially with distance away from roadsides and smelters (Cannon and Bowles, 1962; see also Chapter 8). This deposited lead is persistent. It is neither washed

of the same types of crops taken from actual agricultural situations by Wolnik et al. (1983). Dedolph et al. (1970) found that while ryegrass and radish leaves grown near a busy highway contained deposited airborne lead, the edible portion of the radish was unaffected by variations in either soil lead or air lead.

To estimate the distribution of natural and atmospheric lead in food crops (Table 7-9), it is necessary to recognize that some crops of the Wolnik et al. study have no lead from direct atmospheric deposition, that all lead comes through soil moisture. The lowest concentrations of lead are found in those crops where the edible portion grows above ground and is protected from atmospheric deposition (sweet corn and tomatoes). Belowground crops are also protected from atmospheric deposition but have slightly higher concentrations of lead, partly because lead accumulates in the roots of plants (potatoes, onions, carrots). Leafy aboveground plants (lettuce, spinach, wheat) have even higher lead concentrations presumably because of exposure to atmospheric lead. The assumption that can be made here is that, in the absence of atmospheric deposition, exposed aboveground plant parts would have lead concentrations similar to protected aboveground parts.

The data on these ten crops suggest that root vegetables have lead concentrations between 0.0046 and 0.009 μg/g, all soil lead, which presumably is half natural and half anthropogenic (called indirect atmospheric lead here). Aboveground parts not exposed to significant amounts of atmospheric deposition (sweet corn and tomatoes) have less lead internally, also equally divided between natural and indirect atmospheric lead. If it is assumed that this same concentration is the internal concentration for aboveground parts for other plants, it is apparent that five crops have direct atmospheric deposition in proportion to surface area and estimated duration of exposure. The deposition rate of 0.04 ng/cm^2·day in rural environments (see Section 6.4.1) could account for these amounts of direct atmospheric lead.

In this scheme, soybeans and peanuts are anomalously high. Peanuts grow underground in a shell and should be of a lead concentration similar to potatoes or carrots, although peanuts technically grow from the stem of a plant. Soybeans grow inside a sheath and should have an internal lead concentration similar to corn. The fact that both soybeans and peanuts are legumes may indicate species differences.

The accumulation of lead in edible crops was measured by Ter Haar (1970), who showed that edible plant parts not exposed to air (potatoes, corn, carrots, etc.) do not accumulate atmospheric lead, while leafy vegetables do. Inedible parts, such as corn husks, wheat and oat chaff, and soybean hulls were also contaminated. These results were confirmed by McLean and Shields (1977), who found that most of the lead in food crops is on leaves and husks. The general conclusion from these studies is that lead in food crops varies according to exposure to the atmosphere and in proportion to the effort taken to separate husks, chaff, and hulls from edible parts during processing for human or animal consumption.

These discussions lead to the conclusion that root parts and protected aboveground parts of edible crops contain natural lead and indirect atmospheric lead, both derived from the soil. For exposed aboveground parts, any lead in excess of the average found on unexposed aboveground parts is considered to be the result of direct atmospheric deposition.

Near smelters, Merry et al. (1981) found a pattern different from roadside studies cited above. They observed that wheat crops contained lead in proportion to the amount of soil lead, not vegetation surface contamination. A similar effect was reported by Harris (1981).

7.2.2.2.2 Livestock. Lead in forage was found to exceed 950 µg/g within 25 m of roadsides with 15,000 or more vehicles per day (Graham and Kalman, 1974. At lesser traffic densities, 200 µg/g were found. Other reports have observed 20 to 660 µg/g with the same relationship to traffic density and distance from the road (see review by Graham and Kalman, 1974). A more recent study by Crump and Barlow (1982) showed that the accumulation of lead in forage is directly related to the deposition rate, which varied seasonally according to traffic density. The deposition rate was measured using the moss bag technique, in which bags of moss are exposed and analyzed as relative indicators of deposition flux. Rain was not effective in removing lead from the surface of the moss.

7.2.3 Lead in Surface and Ground Water

Lead occurs in untreated water in either dissolved or particulate form. Dissolved lead is operationally defined as that which passes through a 0.45 µm membrane filter. Because atmospheric lead in rain or snow is retained by soil, there is little correlation between lead in precipitation and lead in streams which drain terrestrial watersheds. Rather, the important factors seem to be the chemistry of the stream (pH and hardness) and the volume of the stream flow. For groundwater, chemistry is also important, as is the geochemical composition of the water-bearing bedrock.

Of the year-round housing units in the United States, 84 percent receive their drinking water from a municipal or private supply of chemically treated surface or ground water. The second largest source is privately owned wells (Bureau of the Census, 1982). In some communities, the purchase of untreated bottled drinking water is a common practice. The initial concentration of lead in this water, depends largely on the source of the untreated water.

7.2.3.1. Typical Concentrations of Lead in Untreated Water.

7.2.3.1.1 Surface water. Durum et al. (1971) reported a range of 1 to 55 µg/l in 749 surface water samples in the United States. Very few samples were above 50 µg/l, and the average was 3.9 µg/l. Chow (1978) reviewed other reports with mean values between 3 and 4 µg/l. The National Academy of Sciences (1980) reported a mean of 4 µg/l with a range from below detection to 890 µg/l. Concentrations of 100 µg/l were found near sites of sewage treatment, urban runoff, and industrial waste disposal.

Because 1 µg/l was at or below the detection limit of most investigators during the 1970's, it is likely that the mean of 3 to 4 µg/l was unduly influenced by a large number of erroneously high values at the lower range of detection. On the other hand, Patterson (1980) reports values of 0.006 to 0.05 µg/l for samples taken from remote streams. Extreme care was taken to avoid contamination and analytical techniques sensitive to less than 0.001 µg/l were used.

Streams and lakes are influenced by their water chemistry and the lead content of their sediments. At neutral pH, lead moves from the dissolved to the particulate form and the particles eventually pass to sediments. At low pH, the reverse pathway generally takes place. Hardness, which is a combination of the Ca and Mg concentration, also can influence lead concentrations. At higher concentrations of Ca and Mg, the solubility of lead decreases. Further discussion of the chemistry of lead in water may be found in Sections 6.5.2.1 and 8.2.2.

7.2.3.1.2 Ground water. Municipal and private wells account for a large percentage of the drinking water supply. This water typically has a neutral pH and somewhat higher hardness than surface water. Lead concentrations are not influenced by acid rain, surface runoff, or atmospheric deposition. Rather, the primary determinant of lead concentration is the geochemical makeup of the bedrock that is the source of the water supply. Ground water typically ranges from 1 to 100 µg Pb/l (National Academy of Sciences, 1980). Again, the lower part of the range may be erroneously high due to difficulties of analysis. It is also possible that the careless application of fertilizers or sewage sludge to agricultural lands can cause contamination of ground water supplies.

7.2.3.1.3 Natural vs. anthropogenic lead in water. Although Chow (1978) reports that the natural lead concentration of surface water is 0.5 µg/l, this value may be excessively high. In a discussion of mass balance considerations (National Academy of Sciences, 1980), natural lead was suggested to range from 0.005 to 10 µg/l. Patterson (1980) used further arguments to establish an upper limit of 0.02 µg/l for natural lead in surface water. This upper limit will be used in further discussions of natural lead in drinking water.

Because ground water is free of atmospheric lead, lead in ground water should probably be considered natural in origin as it occurs at the well head, unless there is evidence of surface contamination.

7.2.3.2 Human Consumption of Lead in Water. Whether from surface or ground water supplies, municipal waters undergo extensive chemical treatment prior to release to the distribution system. There is no direct effort to remove lead from the water supply. However, some treatments, such as flocculation and sedimentation, may inadvertently remove lead along with other undesirable substances. On the other hand, chemical treatment to soften water increases the solubility of lead and enhances the possibility that lead will be added to water as it passes through the distribution system.

7.2.3.2.1 Contributions to drinking water. For samples taken at the household tap, lead concentrations are usually higher in the initial volume (first daily flush) than after the tap has been running for some time. Water standing in the pipes for several hours is intermediate between these two concentrations (Sharrett et al., 1982; Worth et al., 1981). Common plumbing materials are galvanized and copper pipe; lead solder is usually used to seal the joints of copper pipes. Lead pipes are seldom in service in the United States, except in the New England states (Worth et al., 1981).

Average lead content of running water at the household tap is generally lower (8 µg/l) than in some untreated water sources (25 to 30 µg/l) (Sharrett et al., 1982). This implies either that treatment can remove a portion of the lead or that measurements of untreated water are erroneously high. If first flush or standing water is sampled, the lead content may be considerably higher. Sharrett et al. (1982) showed that in both copper and galvanized pipes, lead concentrations were increased by a factor of two when the sample was taken without first flushing the line (see Section 7.3.1.3).

The age of the plumbing is an important factor. New copper pipes with lead solder exposed on the inner surface of the joints produce the highest amount of lead in standing water. After six years, this lead is leached away and copper pipes subsequently have less lead in standing water than galvanized pipes. Because lead pipes are rarely used in the United States, exposure from this source will be treated as a special case in Section 7.3.2.1. The pH of the water is also important; the acid water of some eastern United States localities can increase the leaching rate of lead from lead pipes or lead solder joints and prevent the buildup of a protective coating of calcium carbonate plaque.

Table 7-10 summarizes the contribution of atmospheric lead to drinking water. In this determination, the maximum reported value for natural lead (0.02 µg/l) was used, all additional lead in untreated water is considered to be of atmospheric origin, and it is assumed that treatment removes 85 percent of the original lead, and that any lead added during distribution is non-atmospheric anthropogenic lead.

7.2.3.2.2 Contributions to food. The use of treated water in the preparation of food can be a significant source of lead in the human diet. There are many uncertainties in determining this contribution, however. Water used in food processing may be from a municipal supply or a private well. This water may be used to merely wash the food, as with fruits and vegetables, or as an actual ingredient. Water lead may remain on food that is partially or entirely dehydrated during processing (e.g., pasta). Water used for packing or canning may be used with the meal or drained prior to preparation. It is apparent from discussions in Section 7.3.1.3 that, considering both drinking water and food preparation, a significant amount of lead can be consumed by humans from treated water. Only a small fraction of this lead is of atmospheric origin, however.

TABLE 7-10. SUMMARY OF LEAD IN DRINKING WATER SUPPLIES*

	Natural Pb	Indirect atmospheric Pb	Direct atmospheric Pb	Non-atmospheric anthropogenic Pb	Total Pb
Untreated					
Lakes	0.02	15	10	--	25
Rivers	0.02	15	15	--	30
Streams	0.02	2.5	2.5	--	5
Groundwater	3	--	--	--	3
Treated					
Surface	0.003	2.5	1.5	4	8
Ground	0.45	--	--	7.5	8

*units are μg/l.

7.2.4 Summary of Environmental Concentrations of Lead

Lead concentrations in environmental media that are in the pathway to human consumption are summarized on Table 7-11. These values are estimates derived from the preceding discussions. In each category, a single value is given, rather than a range, in order to facilitate further estimates of actual human consumption. This use of a single value is not meant to imply a high degree of certainty in its determination or homogeneity within the human population. The units for water are converted from μg/l as in Table 7-10 to μg/g to facilitate the discussions of dietary consumption of water and beverages.

TABLE 7-11. SUMMARY OF ENVIRONMENTAL CONCENTRATIONS OF LEAD

Medium	Natural Pb	Atmospheric Pb	Total Pb
Air urban ($\mu g/m^3$)	0.00005	0.8	0.8
rural ($\mu g/m^3$)	0.00005	0.2	0.2
Soil total (μg/g)	8-25	3.0	15.0
Food crops (μg/g)	0.0025	0.027	0.03
Surface water (μg/g)*	0.00002	0.005	0.005
Ground water (μg/g)*	0.003	--	0.003

*note change in units from Table 7-12.

Because concentrations of natural lead are generally three to four orders of magnitude lower than anthropogenic lead in ambient rural or urban air, all atmospheric contributions of lead are considered to be of anthropogenic origin. Natural soil lead typically ranges from 10 to 30 μg/g, but much of this is tightly bound within the crystalline matrix of soil minerals at normal soil pHs of 4 to 8. Lead in the organic fraction of soil is part natural and part atmospheric. The fraction derived from fertilizer is considered to be minimal. In undisturbed rural and remote soils, the ratio of natural to atmospheric lead is about 1:1, perhaps as high as 1:3. This ratio persists in soil moisture and in internal plant tissues. Thus, some of the internal lead in crops is of anthropogenic origin, and some is natural. Information on the effect of fertilizer on this ratio is not available. Lead in untreated surface water is 99 percent anthropogenic, presumably atmospheric except near municipal waste outfalls. It is possible that 75 percent of this lead is removed during treatment. Lead in untreated ground water is probably all natural.

In tracking air lead through pathways to human exposure, it is necessary to distinguish between lead of atmospheric origin that has passed through the soil (indirect atmospheric lead), and atmospheric lead that has deposited directly on crops or water. Because indirect atmospheric lead will remain in the soil for many decades, this source is insensitive to projected changes in atmospheric lead concentrations. Regulation of ambient air lead concentrations will not affect indirect atmospheric lead concentrations over the next several decades.

The method of calculating the relative contribution of atmospheric lead to total potential human exposure relies heavily on the relationship between air concentration and deposition flux described on Section 6.4. Estimates of contributions from other sources are usually based on the observed value for total lead concentration from which the estimated contribution of atmospheric lead is subtracted. Except for the contribution of lead solder in food cans and paint pigments in dust, there is little or no direct evidence for the contribution of nonatmospheric anthropogenic lead to the total lead consumption of humans.

7.3 POTENTIAL PATHWAYS TO HUMAN EXPOSURE

The preceding section discussed ambient concentrations of lead in the environment, focusing on levels in the air, soil, food crops, and water. In this section, environmental lead concentrations are examined from the perspective of pathways to human exposure (Figure 7-1). Initially, a current baseline exposure scenario is described for an individual with a minimum amount of daily lead consumption. This person would live and work in a nonurban environment, eat a normal diet of food taken from a typical grocery shelf, and would have no habits or activities that would tend to increase lead exposure. Lead exposure at the baseline level is

considered unavoidable without further reductions of lead in the atmosphere or in canned foods. Most of the baseline lead is of anthropogenic origin, although a portion is natural, as discussed in Section 7.3.1.5.

7.3.1 Baseline Human Exposure

To arrive at a minimum or baseline exposure for humans, it is necessary to begin with the environmental components, air, soil, food crops, and water, which are the major sources of lead consumed by humans (Table 7-11). These components are measured frequently, even monitored routinely in the case of air, so that many data are available on their concentrations. But there are several factors which modify these components prior to actual human exposure. We do not breathe air as monitored at an atmospheric sampling station, we may be closer to or farther from the source of lead than is the monitor. We may be inside a building, with or without filtered air; the water we drink does not come directly from a stream or river. It has passed through a chemical treatment plant and a distribution system. A similar type of processing has modified the lead levels present in our food.

Besides the atmospheric lead in environmental components, there are two other sources that contribute to this baseline of human exposure: paint pigments and lead solder (Figure 7-6). Solder contributes directly to the human diet through canned food and copper water distribution systems. Chips of paint pigments are discussed later under special environments. But paint and solder are also a source of lead-bearing dusts. The most common dusts in the baseline human environment are street dusts and household dusts. They originate as emissions from mobile or stationary sources, as the oxidation products of surface exposure, or as products of frictional grinding processes. Dusts are different from soil in that soil derives from crustal rock and typically has a lead concentration of 10 to 30 μg/g, whereas dusts come from both natural and anthropogenic sources and vary from 1,000 to 10,000 μg/g.

The discussion of the baseline human exposure traces the sequence from ambient air to inhaled air, from soil to prepared food, from natural water to drinking water, and from paint, solder and aerosol particles to dusts. At the end of this section, Table 7-24 summarizes the four sources by natural and anthropogenic contributions, with the atmospheric contribution to the anthropogenic fraction identified. Reference to this table will guide the discussion of human exposure in a logical sequence that ultimately presents an estimate of the exposure of the human population to atmospheric lead. To construct this table, it was necessary to make decisions based on sound scientific judgment, occasionally in the absence of conclusive data. This method provides a working approach to identifying sources of lead that can be easily modified as more accurate data become available.

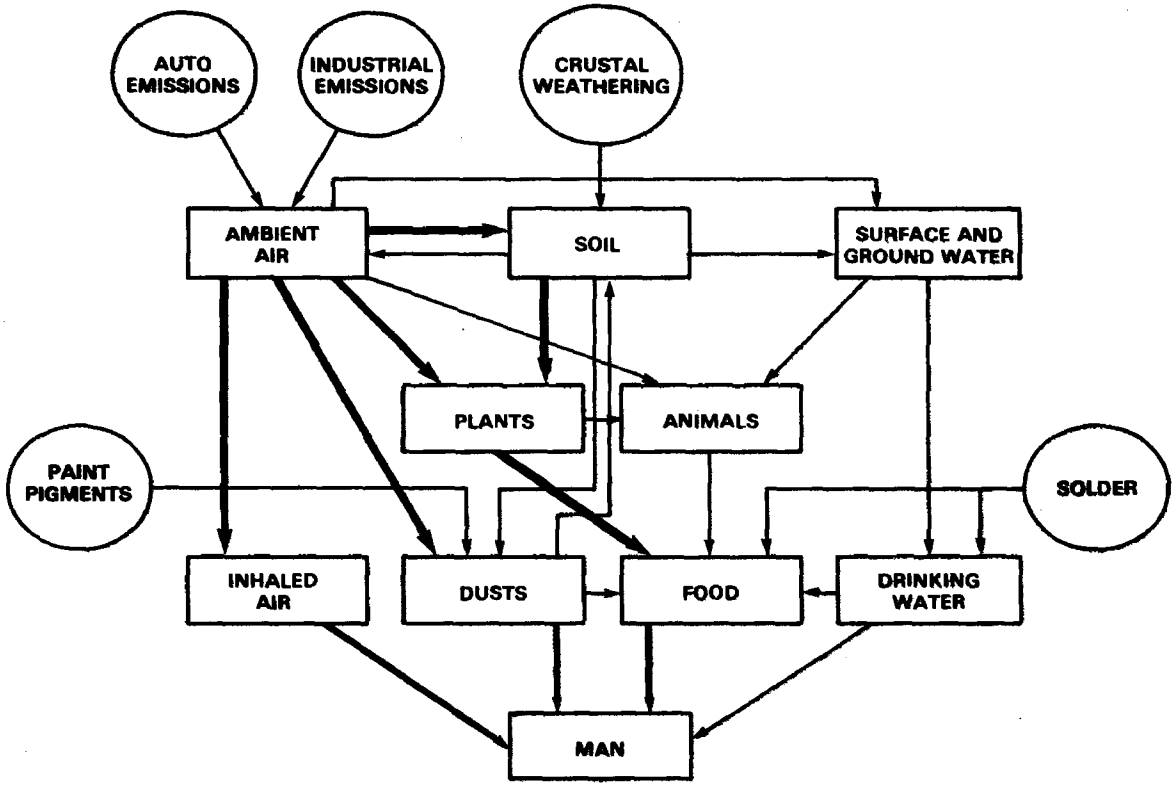

Figure 7-6. Paint pigments and solder are two additional sources of patential lead exposure which are not of atmospheric origin. Solder is common even in baseline exposures and may represent 30 to 45 percent of the baseline human consumption. Paint pigments are encountered in older houses and in soils adjacent to older houses.

7.3.1.1 Lead in Inhaled Air. A principal determinant of atmospheric lead is distance from the source. At more than 100 m from a major highway or more than 2 km from a stationary source, lead concentrations generally drop to constant levels (see Section 6.3), and the particle size distribution shifts from a bimodal distribution to a unimodal one with a mass median equivalent diameter of about 0.2 μm. Because the concentration of atmospheric lead at nonurban stations is generally from 0.05 to 0.15 μg/m^3, a value of 0.1 μg/m^3 may reasonably be assumed. A correction can be made for the indoor/outdoor ratio assuming the average individual spends 20-22 hours/day in an unfiltered inside atmosphere and the average indoor/outdoor ratio for a nonurban location is 0.5 (Table 7-7). The adjusted air concentration becomes 0.05 μg/m^3 for baseline purposes.

The concentration of natural lead in the atmosphere, discussed in Section 7.2.1.1.3, is probably about 0.00005 μg/m^3. This is an insignificant amount compared to the anthropogenic contribution of 0.2 μg/m^3. A summary of lead in inhaled air appears in Table 7-12.

TABLE 7-12. SUMMARY OF INHALED AIR LEAD EXPOSURE

	Adjusted air Pb conc.[1] μg/m^3	Amount inhaled (m^3/day)	Total lead exposure (μg/day)	Natural Pb (μg/day)	Direct atmospheric Pb (μg/day)
Children (2 year-old)	0.05	10	0.5	0.001	0.5
Adult-working inside	0.05	20	1.0	0.002	1.0
Adult-working outside	0.10	20	2.0	0.004	2.0

[1]Values adjusted for indoor/outdoor ratio of lead concentrations and for daily time spent outdoors.

7.3.1.2 Lead in Food. The route by which many people receive the largest portion of their daily lead intake is through foods. Several studies have reported average dietary lead inakes in the range 100 to 500 μg/day for adults, with individual diets covering a much greater range (Schroeder and Tipton, 1968; Tepper, 1971; Mahaffey, 1978; Nutrition Foundation, Inc. 1982). Gross (1981) analyzed results of the extensive lead mass balance experiments described by Kehoe (1961), which were conducted from 1937 to 1972. According to these data, total dietary lead intake decreased from approximately 300 μg/day in 1937 to 100 μg/day in 1970, although there is considerable variability in the data. Only a fraction of this lead is absorbed, as discussed in Chapter 10.

The amount of lead typically found in plants and animals is discussed in Section 7.2.2.2. The sources of this lead are air, soil, and untreated waters (Figure 7-1). Food crops and livestock contain lead in varying proportions from the atmosphere and natural sources. From the farm to the dinner table, lead is added to food as it is harvested, transported, processed, packaged, and prepared. The sources of this lead are dusts of atmospheric and industrial origin, metals used in grinding, crushing, and sieving, solder used in packaging, and water used in cooking.

The American diet is extremely complex and variable among individuals. Pennington (1983) has described the basic diets, suppressing individual variation but identifying 234 typical food categories, for Americans grouped into eight age/sex groups (Table 7-13). These basic diets are the foundation for the Food and Drug Administration's revised Total Diet Study, often called the market basket study, beginning in April, 1982. The diets used for this discussion include food, beverages and drinking water for a 2-year-old child, the adult female 25 to 30 years of age and the adult male 25 to 30 years of age. The 234 typical foods that comprise the basic diets approximate 90 percent or more of the food actually consumed by participants in the two surveys which formed the basis of the Pennington study. These 234 categories have been further reduced to 26 food categories (Table 7-13) and 6 beverage categories (Table 7-20) based on known or presumed similarities in lead concentration, and a weighted average lead concentration has been assigned to each category from available literature data. A complete list of the Pennington categories and the rationale for grouping into the categories of Tables 7-13 and 7-20 appears in Tables 7D-1 and 7D-2 of Appendix 7D.

Milk and foods are treated separately from water and other beverages because the pathways by which lead enters these dietary components are substantially different (Figure 7-1), as solder and atmospheric lead contribute significantly to each. Data for lead concentrations on Tables 7-13 and 7-20 came from a preliminary report of the 1982 Total Diet Study provided by the U.S. Food and Drug Administration (1983) for the purpose of this document. In 1982, the Nutrition Foundation published an exhaustive study of lead in foods, using some data from the National Food Processors Assocation and some data from Canadian studies by Kirkpatrick et al. (1980) and Kirkpatrick and Coffin (1974, 1977). A summary of the available data for the period 1973 to 1980 was prepared in an internal report to the FDA prepared by Beloian (1980). Portions of these reports were used to interpret the contributions of lead to food during processing.

Many of the food categories in Table 7-13 correspond directly to the background crop and meat data presented in Table 7-9. The following section evaluates the amounts of lead added during each step of the process from the field to the dinner table. In the best case, re-

liable data exist for the specific situation in question and conclusions are drawn. In some cases, comparable data can be used with a few reasonable assumptions to formulate acceptable estimates of lead contributions. For a portion of the diet, there are no acceptable data and the contributions of lead must, for the time, be listed as of undetermined origin.

TABLE 7-13. LEAD CONCENTRATIONS IN MILK AND FOODS

	Dietary consumption (g/day)			Lead concentration* (μg/g)	Summary food category in Table 7-16
	Child (2-yr-old)	Adult female	Adult male		
Milk	350	190	280	0.01	A
Dairy products	24	36	49	0.03	A
Milk as ingredient	7	11	15	0.01	A
Beef	33	61	120	0.035	B
Pork	12	21	40	0.06	B
Chicken	12	20	29	0.02	B
Fish	5	15	18	0.09	B
Prepared Meats	14	11	23	0.013	B
Other Meats	1	7	5	0.07	B
Eggs	33	34	53	0.017	B
Bread	42	56	75	0.015	C
Flour as ingredient	23	26	79	0.013	C
Non-wheat cereals	33	13	34	0.025	C
Corn flour	14	12	20	0.025	C
Leafy vegetables	7	39	38	0.05	C
Root vegetables	3	7	7	0.025	C
Vine vegetables	19	49	62	0.025	C
Canned vegetables	39	53	62	0.25	D
Sweet corn	4	6	7	0.01	C
Canned sweet corn	5	4	7	0.21	D
Potatoes	38	52	85	0.02	C
Vegetable oil	5	12	15	0.03	C
Sugar	15	21	34	0.03	C
Canned fruits	14	11	13	0.22	D
Fresh fruits	49	57	49	0.02	C
Pureed baby food	11	--	--	0.03	
Subtotal	812	824	1219		
Water and beverages	647	1286	1804		See Table 7-21
Total	1459	2110	3023		

*Data are summarized from preliminary data provided by the U.S. FDA; complete data appear in Appendix 7D.

7.3.1.2.1 Lead added during handling and transportation to processor. Between the field and the food processor, lead is added to the food crops. It is assumed that this lead is all of direct atmospheric origin. Direct atmospheric lead can be lead deposited directly on food materials by dry deposition, or it can be lead on dust which has collected on other surfaces, then transferred to foods. For the purposes of this discussion, it is not necessary to distinguish between these two forms, as both are a function of air concentration.

There are no clear data on how much lead is added during transportation, but some observations are worth noting. First, some fresh vegetables (e.g., potatoes, lettuce, carrots, onions) undergo no further processing other than trimming, washing and packaging. If washed, water without soap is used; no additives or preservatives are used. An estimate of the amount of atmospheric lead added during handling and transportation of all food crops can be made from the observed increases in lead on those fresh vegetables where handling and transportation would be the only source of added lead. Because atmospheric lead deposition is a function of time, air concentration, and exposed surface area, there is an upper limit to the maximum amount of direct atmospheric lead that can be added, except by the accumulation of atmospheric dusts.

7.3.1.2.2 Lead added during preparation for packaging. For some of the food items, data are available on lead concentrations just prior to the filling of cans. In the case where the food product has not undergone extensive modification (e.g., cooking, added ingredients), the added lead was most likely derived from the atmosphere or from the machinery used to handle the product. As with transportation, the addition of atmospheric lead is limited to reasonable amounts that can be added during exposure to air, and reasonable amounts of atmospheric dust accumulation on food processing surfaces. One process that may increase the exposure of the food to air is the use of air in separating food items, as in wheat grains from chaff.

Where modification of the food product has occurred, the most common ingredients added are sugar, salt, and water. It is reasonable that water has a lead concentration similar to drinking water reported in Section 7.3.1.3 (0.008 µg/g) and that sugar (Boyer and Johnson, 1982) and salt have lead concentrations of 0.01 µg/g. Grinding, crushing, chopping, and cooking may add lead from the metallic parts of machinery and from industrial greases. A summary of the data (Table 7-14) indicates that about 30 percent of the total lead in canned goods is the result of prepacking processes.

7.3.1.2.3 Lead added during packaging. From the time a product is packaged in bottles, cans or plastic containers, until it is opened in the kitchen, it may be assumed that no food item receives atmospheric lead. Most of the lead which is added during this stage comes from the solder used to seal some types of cans. Estimates by the U.S. FDA, prepared in cooperation

with the National Food Processors Association, suggest that lead in solder contributes more than 66 percent of the lead in canned foods where a lead solder side seam was used. This lead was thought to represent a contribution of 20 percent to the total lead consumption in foods (F.R., 1979 August 31).

TABLE 7-14. ADDITION OF LEAD TO FOOD PRODUCTS

Food	In the field	After preparation for packaging	After packaging	After kitchen preparation	Total Pb added after harvest
Soft Packaged					
Wheat	0.037		0.065	--	--
Field corn	0.022		0.14	0.025	0.003
Potatoes	0.009		0.018	0.02	0.011
Lettuce	0.013		0.07	0.015	0.002
Rice	0.007		0.10	0.084	0.077
Carrots	0.009		0.05	0.017	0.008
Beef	0.01		0.07	0.035	0.025
Pork	0.06		0.10	0.06	--
Metal cans					
Sweet corn	0.003	0.04	0.27	0.28	0.28
Tomatoes	0.002	0.06	0.29	--	
Spinach	0.045	0.43	0.68	0.86	0.82
Peas		0.08	0.19	0.22	0.14
Applesauce		0.08	0.24	0.17	0.09
Apricots		0.07	0.17	--	0.10
Mixed fruit		0.08	0.24	0.20	0.12
Plums		0.09	0.16		0.07
Green beans		0.16	0.32	0.16	--

This table summarizes the stepwise addition of lead to food products at several stages between the field and the dinner table. Data are in µg/g fresh weight.

The full extent of the contribution of the canning process to overall lead levels in albacore tuna was reported in a benchmark study by Settle and Patterson (1980). Using rigorous clean laboratory procedures, these investigators analysed lead in fresh tuna, as well as in tuna packaged in soldered and unsoldered cans. The data, presented in Table 7-15, show that lead concentrations in canned tuna are elevated above levels in fresh tuna by a factor of 4,000, and by a factor of 40,000 above natural levels of lead in tuna. Nearly all of the increase results from leaching of the lead from the soldered seam of the can; tuna from an unsoldered can is elevated by a factor of only 20 compared with tuna fresh from the sea. Note

that when fresh tuna is dried and pulverized, as in the National Bureau of Standards reference material, lead levels are seen to increase by a factor of 400 over fresh sea tuna. Table 7-15 also shows the results of analyses conducted by the National Marine Fisheries Service.

TABLE 7-15. PREHISTORIC AND MODERN CONCENTRATIONS IN HUMAN FOOD FROM A MARINE FOOD CHAIN[1]

	Estimated prehistoric	Modern
Surface seawater	0.0005	0.005
Albacore muscle, fresh	0.03	0.3
Albacore muscle from die-punched unsoldered can	--	7.0
Albacore muscle, lead-soldered can	--	1400
Anchovy from albacore stomach	2.1	21
Anchovy from lead-soldered can	--	4200

[1]Values are ng/g fresh weight.

Source: Settle and Patterson (1980).

7.3.1.2.4 Lead added during kitchen preparation and storage. Although there have been several studies of the lead concentrations in food after typical meal preparation, most of the data are not amenable to this analysis. As a part of its compliance program, the U.S. FDA has conducted the Total Diet Study of lead and other trace contaminants in kitchen-prepared food each year since 1973. Because the kitchen-prepared items were composited by category, there is no direct link between a specific food crop and the dinner table. Since April, 1982, this survey has analyzed each food item individually (Pennington, 1983).

Other studies which reflect contributions of lead added during kitchen preparation have been conducted. Capar (1978) showed that lead in acidic foods that are stored refrigerated in open cans can increase by a factor of 2 to 8 in five days if the cans have a lead-soldered side seam not protected by an interior lacquer coating. Comparable products in cans with the lacquer coating or in glass jars showed little or no increase.

7.3.1.2.5 Recent changes of lead in food. As a part of its program to reduce the total lead intake by children (0 to 5 years) to less than 100 μg/day by 1988, the U.S. FDA estimated lead intakes for individual children in a large-scale food consumption survey (Beloian and McDowell, 1981). To convert the survey of total food intakes into lead intake, 23 separate government and industry studies, covering the period from 1973 to 1978, were statistically analyzed. In spite of the variability that can occur among individuals grouped by age, the authors estimated a baseline (1973-78) daily lead intake of 15 μg/day for infants aged 0 to 5 months, 59 μg/day for children 6 to 23 months, and 82 μg/day for children 2 to 5 years. Between 1973 and 1978, intensive efforts were made by the food industry to remove sources of lead from infant food items. By 1980, there had been a 47 percent reduction in the lead consumption of the age group 0 to 5 months and a 7 percent reduction for the 6 to 23 month age group (Table 7-16). Most of this reduction was accomplished by the discontinuation of soldered cans used for infant formula.

TABLE 7-16. RECENT TRENDS OF LEAD CONCENTRATIONS IN FOOD ITEMS

	Early 70's (μg/g)	1976-77 (μg/g)	1980-81 (μg/g)	1982 (μg/g)
Canned food[1]				
Green beans	0.32		0.32	0.16
Beans w/pork	0.64	data	0.26	0.17
Peas	0.43	not	0.19	0.22
Tomatoes	0.71	available	0.29	---
Beets	0.38		0.24	0.12
Tomato juice	0.34		0.08	0.067
Applesauce	0.32		0.04	0.17
Citrus juice	0.14		0.11	0.04
Infant food[2]				
Formula concentrate	0.10	0.055	0.01	
Juices	0.30	0.045	0.015	
Pureed foods	0.15	0.05	0.02	
Evaporated milk	0.52	0.10	0.07	

[1]Boyer and Johnson (1982); 1982 data from U.S. Food and Drug Administration (1983).
[2]Pre-1982 data from early 70's and 1976-79 from Jelinek (1982); 1980-81 data from Schaffner et al. (1983).

The 47 percent reduction in dietary lead achieved for infants prior to 1980 came about largely because there are relatively few manufacturers of foods for infants and it was comparatively simple for this industry to mount a coordinated program in cooperation with the U.S.

FDA. There has not yet been a similar decrease in adult foods (Table 7-16) because only a few manufacturers have switched to non-lead cans. As the switchover increases, lead in canned food should decrease to a level as low as 30 percent of the pre-1978 values, and there should be a corresponding decrease of lead in the total adult diet, perhaps as much as 25 to 30 percent. The use of lead-soldered cans in the canning industry has decreased from 90 percent in 1979 to 63 percent in 1982. By the end of 1984, the two leading can manufacturers expect to produce no more lead-soldered cans for the food industry. A two-year time lag is expected before the last of these cans disappears from the grocery shelf. Some of the 23 smaller manufacturers of cans have announced similar plans over a longer period of time. It is likely that any expected decrease in the contribution of air lead to foods will be complemented by a decrease in lead from soldered cans.

7.3.1.2.6 Summary of lead in food. The data of Table 7-13 have been condensed to four categories from the 26 categories of food in Table 7-17. The total lead concentrations are weighted according to consumption from Table 7-13, then broken down by source based on the information provided in Tables 7-9 and 7-14, which show estimates of the atmospheric lead added before and after harvest. The same weighted total lead concentrations are used to estimate milk and food lead consumption in Table 7-18 for three age/sex categories. The total dietary lead consumption is then broken down by source in Table 7-19, using the distributions of Table 7-17. Because the percent distribution by source is approximately the same for the three age/sex categories, only the data for adult males are shown.

TABLE 7-17. SUMMARY OF LEAD CONCENTRATIONS IN MILK AND FOODS BY SOURCE*

Major food category	Total lead	Direct atmospheric lead	Pb from solder & other metals	Pb of undetermined origin	% Direct atmospheric lead
A. Dairy	0.013	0.007	--	0.007	54%
B. Meat	0.036	0.02	0.02	0.016	56%
C. Food crops	0.022	0.016	--	0.002	73%
D. Canned food	0.24	0.016	0.20	0.02	7%

*Foods have been categorized from Table 7-13. Data are in μg/g. The natural and indirect atmospheric lead concentrations in dairy and meat products are estimated to be 0.0002 μg/g from each source. In food crops and canned foods, these values are 0.002 μg/g.

It is apparent that at least 35 percent of lead in milk and food can be attributed to direct atmospheric deposition, compared to 26 percent from solder or other metal sources. Of the remaining 34 percent for which the source is as yet undetermined, it is likely that further research will show this lead to be part atmospheric in origin and part from solder and other industrial metals.

This dietary lead consumption is used to calculate the total baseline human exposure in Section 7.3.1.5 and is the largest baseline source of lead. Possible additions to dietary lead consumption are discussed in Section 7.3.2.1.1 with respect to urban gardens.

TABLE 7-18. SUMMARY BY AGE AND SEX OF ESTIMATED AVERAGE LEVELS OF LEAD INGESTED FROM MILK AND FOODS

	Dietary consumption (g/day)			Lead conc. in food	Lead consumption µg/day		
	2-yr-old child	Adult female	Adult male	µg Pb/g*	2-yr-old child	Adult female	Adult male
A. Dairy	381	237	344	0.013	5.0	3.1	4.5
B. Meat	113	169	288	0.036	4.1	6.1	10.4
C. Food crops	260	350	505	0.022	5.7	7.7	11.1
D. Canned food	58	68	82	0.24	13.9	16.3	19.7
Total	812	824	1219		28.7	33.2	45.6

*Weighted average lead concentration in foods from Table 7-13.

Because the U.S. FDA is actively pursuing programs to remove lead from adult foods, it is probable that there will be a decrease in total dietary lead consumption over the next decade independent of projected decreases in atmospheric lead concentration. With both sources of lead minimized, the lowest reasonable estimated dietary lead consumption would be 10 to 15 µg/day for adults and children. This estimate is based on the assumption that about 90 percent of the direct atmospheric lead, solder lead and lead of undetermined origin would be removed from the diet, leaving 8 µg/day from these sources and 3 µg/day of natural and indirect atmospheric lead.

7.3.1.3 Lead in Drinking Water. The U.S. Public Health Service standards specify that lead levels in drinking water should not exceed 50 µg/l. The presence of detectable amounts of lead in untreated public water supplies was shown by Durum (1971) to be widespread, but only a few samples contained amounts above the 50 µg/l standard.

The major source of lead contamination in drinking water is the water supply system itself. Water that is corrosive can leach considerable amounts of lead from lead plumbing and lead compounds used to join pipes. Moore (1977) demonstrated the effect of water standing in pipes overnight. Lead concentrations dropped significantly with flushing at 10 l/min for five minutes (Figure 7-7). Lead pipe currently is in use in some parts of New England for water service lines and interior plumbing, particularly in older urban areas. The contributions of lead plumbing to potential human exposure are considered additive rather than baseline and are discussed in Section 7.3.2.1.3.

There have been several studies in North America and Europe of the sources of lead in drinking water. A recent study in Seattle, WA by Sharrett et al. (1982) showed that the age of the house and the type of plumbing determined the lead concentration in tap water. Standing water in copper pipes from houses newer than five years averaged 31 µg/l; those less than 18 months average about 70 µg/l. Houses older than five years and houses with galvanized pipe averaged less than 6 µg/l. The source of the water supply, the length of the pipe and the use of plastic pipes in the service line had little or no effect on the lead concentrations. It appears certain that the source of lead in new homes with copper pipes is the solder used to join these pipes, and that this lead is eventually leached away with age.

The Sharrett et al. (1982) study of the Seattle population also provided data on water and beverage consumption which extended the scope of the Pennington (1983) study of all Americans. While the total amount of liquids consumed was slightly higher in Seattle (2200 g/day vs. 1800 g/day for all Americans), the breakdown between water consumed inside and outside the home can prove useful. Men, women and children consume 53, 87, and 87 percent respectively of their water and beverages within the home.

Bailey and Russell (1981) have developed a model for population exposure to lead in home drinking water. The model incorporates data for lead concentration as a function of stagnation time in the pipes, as well as probability distributions for times of water use throughout the day. Population surveys conducted as part of the United Kingdom Regional Heart Survey provided these water-use distributions.

Other studies have been conducted in Canada and Belgium. Lead levels in water boiled in electric kettles were measured in 574 households in Ottawa (Wigle and Charlebois, 1978). Concentrations greater than 50 µg/l were observed in 42.5 percent of the households, and excessive lead levels were associated with kettles more than five years old.

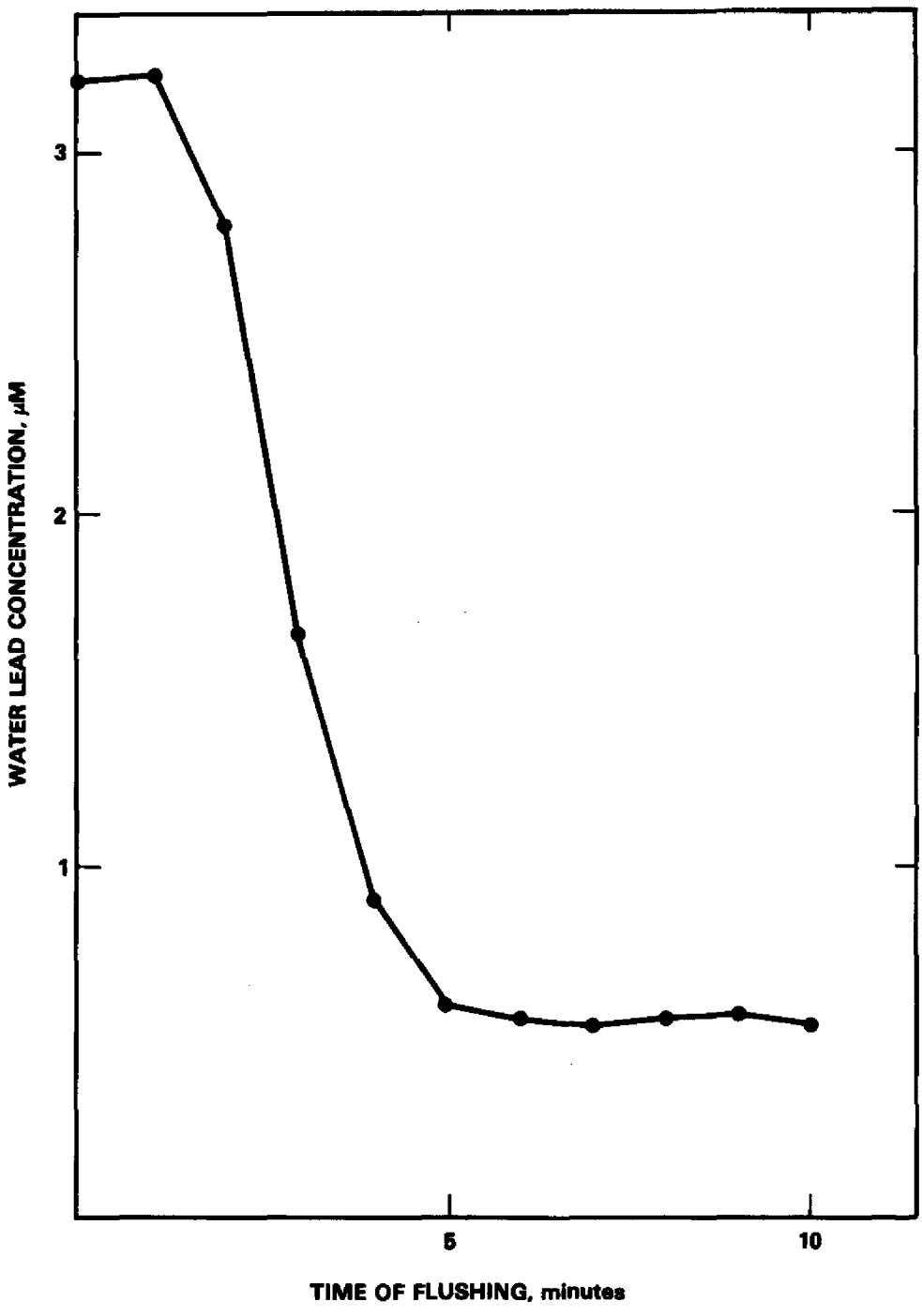

Figure 7-7. Change in drinking water lead concentration in a house with lead plumbing for the first use of water in the morning. Flushing rate was 10 liters/minute.

Source: Moore (1977).

TABLE 7-19. SUMMARY BY SOURCE OF LEAD CONSUMED FROM MILK AND FOODS*

	Total lead	Natural lead	Atmospheric lead		Pb from solder and other metals	Lead of undetermined origin
			Indirect lead	Direct lead		
A. Dairy	4.5	0.1	0.1	2.3	--	2.0
B. Meat	10.4	0.1	0.1	5.7	--	4.5
C. Food crops	11.1	1.0	1.0	8.1	--	1.0
D. Canned foods	19.7	0.2	0.2	1.3	16.4	1.6
Total	45.7	1.4	1.4	17.4	16.4	9.1
% of total	100%	3.1%	3.1%	38.1%	35.9%	19.9%

*Distribution based on adult male diet. Data are in µg/day. There may be some direct atmospheric lead and solder lead in the category of undetermined origin.

The potential exposure to lead through water and beverages is presented in Tables 7-20, 7-21 and 7-22. In Table 7-20, typical concentrations of lead in canned and bottled beverages and in beverages made from tap water (e.g., coffee, tea, drinking water) are shown by source. The baseline concentration of water is taken to be 0.01 µg/g, although 0.006 to 0.008 are often cited in the literature for specific locations. It is assumed that 2/3 of the original lead is lost during water treatment and that only 0.005 µg/g remains from direct atmospheric deposition. The water distribution system adds 0.001 µg/g, shown here as lead of undetermined origin. The source appears to be the pipes or the solder used to seal the pipes. These values are used for water in canned and bottled beverages, with additional amounts added from solder and other packaging procedures.

The lead concentrations in beverages are multiplied by total consumption to get daily lead consumption in Table 7-21 for 3 age/sex categories. For adult males, these are summarized by source of lead in Table 7-22; distribution by source would be proportional for children and adult females. The data of Table 7-22 are used for the overall summary of baseline human exposure in Section 7.3.1.5.

7.3.1.4 Lead in Dusts. By technical definition, dusts are solid particles produced by the disintegration of materials (Friedlander, 1977) and appear to have no size limitations. Although dusts are of complex origin, they may be placed conveniently into a few categories relating to human exposure. Generally, the most convenient categories are household dusts, soil dust, street dusts and occupational dusts. It is a characteristic of dust particles that they accumulate on exposed surfaces and are trapped in the fibers of clothing and carpets. Ingestion of dust particles, rather than inhalation, appears to be the greater problem in the baseline environment, especially ingestion during meals and playtime activity by small children.

TABLE 7-20. SUMMARY BY SOURCE OF LEAD CONCENTRATIONS IN WATER AND BEVERAGES*

	Total lead	Direct atmospheric lead	Lead from solder and other metals	Percent direct atmospheric
Canned juices	0.052	0.0015	0.048	2.9%
Frozen juices	0.02	0.0015	0.014	7.5
Canned soda	0.033	0.0015	0.029	4.5
Bottled soda	0.02	0.0015	0.014	7.5
Canned beer	0.017	0.0015	0.013	8.8
Water & beverages	0.008	0.0015	0.004	18.9

*Data are in µg/g. Natural and indirect atmospheric lead are estimated to be 0.00002 and 0.0025 µg/g respectively, for all beverage types.

TABLE 7-21. DAILY CONSUMPTION AND POTENTIAL LEAD EXPOSURE FROM WATER AND BEVERAGES

Beverage	Consumption* (g/day)			Beverage lead conc.† (µg/g)	Lead consumption (µg/day)		
	2 yr old child	Adult female	Adult male		2 yr old child	Adult female	Adult male
Canned juices	53	28	20	0.052	2.8	1.5	1.0
Frozen juices	66	66	73	0.02	1.3	1.3	1.5
Canned soda	75	130	165	0.033	2.5	4.3	5.4
Bottled soda	75	130	165	0.02	1.5	2.6	3.3
Coffee	2	300	380	0.01	-	3.0	3.8
Tea	32	160	140	0.01	0.3	1.6	1.4
Canned beer	-	35	300	0.017	-	0.6	5.1
Wine	-	35	11	0.01	-	0.1	0.1
Whiskey	-	5	9	0.01	-	0.1	0.1
Water	320	400	510	0.008	2.6	2.6	3.2
Water as ingredient	24	20	31	0.008	0.2	0.2	0.2
Total	647	1286	1804		11.2	17.9	25.1

* Data from Pennington, 1983.
† Data from U.S. Food and Drug Administration, 1983.

TABLE 7-22. SUMMARY BY SOURCE OF LEAD CONSUMED IN WATER AND BEVERAGES*

	Total Pb	Natural and indirect atmospheric Pb	Direct atmospheric Pb	Lead in solder and other metals Pb
Canned juices	1.0	0.05	0.03	0.92
Frozen juices	1.5	0.18	0.11	1.2
Canned soda	5.4	0.42	0.25	4.7
Bottled soda	3.3	0.50	0.3	2.5
Canned beer	5.1	0.8	0.5	3.8
Water & beverages	8.8	2.8	1.6	4.4
Total	25.1	4.8	2.8	17.5
Percent	100%	19.1%	11.1%	69.7%

*Data are for adult males, expressed in µg/day. Percentages are the same for children and adult females. Total consumption for children and adult females shown on Table 7-21.

Two other features of dust are important. First, they must be described in both concentration and amount. The concentration of lead in street dust may be the same in a rural and urban environment, but the amount of dust may differ by a wide margin. Secondly, each category represents some combination of sources. Household dusts contain some atmospheric lead, some paint lead and some soil lead. Street dusts contain atmospheric, soil, and occasionally paint lead. This apparent paradox does not prevent the evaluation of exposures to dust, but it does confound efforts to identify the amounts of atmospheric lead contributed to dusts. For the baseline human exposure, it is assumed that workers are not exposed to occupational dusts, nor do they live in houses with interior leaded paints. Street dust, soil dust and some household dust are the primary sources for baseline potential human exposure.

In considering the impact of street dust on the human environment, the obvious question arises as to whether lead in street dust varies with traffic density. Nriagu (1978) reviewed several studies of lead in street dust. The source of lead was probably flue dust from burning coal. Warren et al. (1971) reported lead in street dust of 20,000 µg/g in a heavily trafficked area. In the review by Nriagu (1978), street dust lead concentrations ranged from 300

to 18,000 µg/g in several cities in the United States. In Hong Kong, lead in street dust ranged from 960 to 7400 µg/g with no direct relationship to traffic volume (Ho, 1979). In other reports from Hong Kong, Lau and Wong (1982) found values from 130 µg/g at 20 vehicles/day to 3,900 µg/g at 37,000 vehicles/day. Fourteen sites in this study showed close correlation with traffic density.

In the United Kingdom, lead in urban and rural street dusts was determined to be 970 and 85 µg/g, respectively, by Day et al. (1975). A later report by this group (Day et al., 1979) discusses the persistency of lead dusts in rainwashed areas of the United Kingdom and New Zealand and the potential health hazard due to ingestion by children. They concluded that, whereas the acidity of rain was insufficient to dissolve and transport lead particles, the potential health hazard lies with the ingestion of these particles during the normal play activities of children residing near these areas. A child playing at a playground near a roadside might consume 20 to 200 µg lead while eating a single piece of candy with unwashed hands. It appears that in nonurban environments, lead in street dust ranges from 80 to 130 µg/g, whereas urban street dusts range from 1,000 to 20,000 µg/g. For the purpose of estimating potential human exposure, an average lead value of 90 µg/g in street dust is assumed for baseline exposure on Table 7-23, and 1500 µg/g in the discussions of urban environments in Section 7.3.2.1.

Dust is also a normal component of the home environment. It accumulates on all exposed surfaces, especially furniture, rugs and windowsills. For reasons of hygiene and respiratory health, many homemakers take great care to remove this dust from the household. Because there are at least two circumstances where these measures are inadequate, it is important to consider the possible concentration of lead in these dusts in order to determine potential exposure to young children. First, some households do not practice regular dust removal, and secondly, in some households of workers exposed occupationally to lead dusts, the worker may carry dust home in amounts too small for efficient removal but containing lead concentrations much higher than normal baseline values.

In Omaha, Nebraska, Angle and McIntire (1979) found that lead in household dust ranged from 18 to 5600 µg/g. In Lancaster, England, a region of low industrial lead emissions, Harrison (1979) found that household dust ranged from 510 to 970 µg/g, with a mean of 720 µg/g. They observed soil particles (10 to 200 µm in diameter), carpet and clothing fibers, animal and human hairs, food particles, and an occasional chip of paint. The previous Lead Criteria Document (U.S. Environmental Protection Agency, 1977) summarized earlier reports of lead in household dust showing residential suburban areas ranging from 280 to 1,500 µg/g, urban residential from 600 to 2,000 µg/g, urban industrial from 900 to 16,000 µg/g. In El Paso, Texas, lead in household dust ranged from 2,800 to 100,000 µg/g within 2 km of a smelter (Landrigan et al. 1975).

It appears that most of the values for lead in dust in nonurban household environments fall in the range of 50 to 500 µg/g. A mean value of 300 µg/g is assumed. The only natural lead in dust would be some fraction of that derived from soil lead. A value of 10 µg/g seems reasonable, since some of the soil lead is of atmospheric origin. Since very little paint lead is included in the baseline estimate, most of the remaining dust lead would be from the atmosphere. Table 7-23 summarizes these estimates of human exposure to dusts for children and adults. It assumes that children ingest about 5 times as much dust as adults, most of the excess being street dusts from sidewalks and playgrounds. Exposure of children to occupational lead would be through contaminated clothing brought home by parents. Most of this lead is of undetermined origin because no data exist on whether the source is dust similar to household dust or unusual dust from the grinding and milling activities of factories.

7.3.1.5 Summary of Baseline Human Exposure to Lead. The values derived or assumed in the preceeding sections are summarized on Table 7-24. These values represent only consumption, not absorption of lead by the human body. The key question of what are the risks to human health from these baseline exposures is addressed in Chapter 13. The approach used here to evaluate potential human exposure is similar to that used by the National Academy of Sciences (1980) and the Nutrition Foundation (1982) in their assessments of the impact of lead in the human environment.

TABLE 7-23. CURRENT BASELINE ESTIMATES OF POTENTIAL HUMAN EXPOSURE TO DUSTS

	Dust lead conc. µg/g	Dust ingested g/day	Dust lead consumed µg/day	Source of lead (µg/day)		
				Natural	Atmos.	Undetermined
Child						
Household dusts	300	0.05	15	0.5	14.5	
Street dust	90	0.04	4.5	-	4.5	
Occupational dust	150	0.01	1.5	0.1	-	1.4
Total		0.10	21.0	0.6	19.0	1.4
Percent			100%	2.8	90.5	6.7
Adult						
Household dusts	300	0.01	3	0.1	2.9	
Street dust	90	-	-	-	-	
Occupational dust	150	0.01	1.5	0.1	-	1.4
Total		0.02	4.5	0.2	2.9	1.4
Percent			100%	4.5	64.4	31.1

TABLE 7-24. SUMMARY OF BASELINE HUMAN EXPOSURES TO LEAD†

Source	Total lead consumed	Soil		Direct atmospheric lead*	Lead from solder or other metals	Lead of undetermined origin
		Natural lead consumed	Indirect atmospheric lead*			
Child-2 yr old						
Inhaled air	0.5	0.001	-	0.5	-	-
Food	28.7	0.9	0.9	10.9	10.3	17.6
Water & beverages	11.5	0.01	2.1	1.2	7.8	-
Dust	21.0	0.6	-	19.0	-	1.4
Total	61.4	1.5	3.0	31.6	18.1	19.0
Percent	100%	2.4%	4.9%	51.5%	29.5%	22.6%
Adult female						
Inhaled air	1.0	0.002	-	1.0	-	-
Food	33.2	1.0	1.0	12.6	11.9	21.6
Water & beverages	17.9	0.01	3.4	2.0	12.5	-
Dust	4.5	0.2	-	2.9	-	1.4
Total	56.6	1.2	4.4	18.5	24.4	23.0
Percent	100%	2.1%	7.8%	32.7%	43.1%	26.8%
Adult male						
Inhaled air	1.0	0.002	-	1.0	-	-
Food	45.7	1.4	1.4	17.4	16.4	31.5
Water & beverages	25.1	0.1	4.7	2.8	17.5	-
Dust	4.5	0.2	-	2.9	-	1.4
Total	76.3	1.7	6.1	24.1	33.9	32.9
Percent	100%	2.2%	8.0%	31.6%	44.4%	27.1%

*Indirect atmospheric lead has been previously incorporated into soil, and will probably remain in the soil for decades or longer. Direct atmospheric lead has been deposited on the surfaces of vegetation and living areas or incorporated during food processing shortly before human consumption.
†Units are in µg/day.

7.3.2 Additive Exposure Factors

There are many conditions, even in nonurban environments, where an individual may increase his lead exposure by choice, habit, or unavoidable circumstance. The following sections describe these conditions as separate exposures to be added as appropriate to the baseline of human exposure described above. Most of these additive exposure clearly derive from air or dust, while few derive from water or food.

7.3.2.1 Living and Working Environments With Increased Lead Exposure. Ambient air lead concentrations are typically higher in an urban than a rural environment. This factor alone can contribute significantly to the potential lead exposure of Americans, through increases in

inhaled air and consumed dust. Produce from urban gardens may also increase the daily consumption of lead. Some environmental exposures may not be related only to urban living, such as houses with interior lead paint or lead plumbing, residences near smelters or refineries, or family gardens grown on high-lead soils. Occupational exposures may also occur in an urban or rural setting. These exposures, whether primarily in the occupational environment or secondarily in the home of the worker, would be additive with other exposures in an urban location or with special cases of lead-based paint or plumbing.

7.3.2.1.1 Urban atmospheres. Urban atmospheres have more airborne lead than do nonurban atmospheres, therefore there are increased amounts of lead in urban household and street dust. Typical urban atmospheres contain 0.5 to 1.0 μg Pb/m^3. Other variables are the amount of indoor filtered air breathed by urban residents, the amount of time spent indoors, and the amount of time spent on freeways. Dusts vary from 500 to 3000 μg Pb/g in urban environments. It is not known whether there is more or less dust in urban households and playgrounds than in rural environments. Whereas people may breathe the same amount of air, eat and drink the same amount of food and water, it is not certain that urban residents consume the same amount of dust as nonurban. Nevertheless, in the absence of more reliable data, it has been assumed that urban and nonurban residents consume the same amount of dusts.

The indoor/outdoor ratio of atmospheric lead for urban environments is about 0.8 (Table 7-7). Assuming 2 hours of exposure/day outdoors at a lead concentration of 0.75 μg/m^3, 20 hours indoors at 0.6 μg/m^3, and 2 hours in a high traffic density area at 5 μg/m^3, a weighted mean air exposure of 1.0 μg/m^3 appears to be typical of urban residents.

7.3.2.1.2 Houses with interior lead paint. In 1974, the Consumer Product Safety Commission collected household paint samples and analyzed them for lead content (National Academy of Sciences; National Research Council, 1976). Analysis of 489 samples showed that 8 percent of the oil-based paints and 1 percent of the water-based paints contained greater than 0.5 percent lead (5000 μg Pb/g paint, based on dried solids), which was the statutory limit at the time of the study. The current statutory limit for Federal construction is 0.06 percent. The greatest amounts of leaded paint are typically found in the kitchens, bathrooms, and bedrooms (Tyler, 1970; Laurer et al., 1973; Gilbert et al., 1979).

Some investigators have shown that flaking paint can cause elevated lead concentrations in nearby soil. For example, Hardy et al. (1971) measured soil lead levels of 2000 μg/g next to a barn in rural Massachusetts. A steady decrease in lead level with increasing distance from the barn was shown, reaching 60 μg/g at fifty feet from the barn. Ter Haar (1974) reported elevated soil lead levels in Detroit near eighteen old wood frame houses painted with lead-based paint. The average soil lead level within two feet of a house was just over 2000 μg/g; the average concentration at ten feet was slightly more than 400 μg/g. The same author

reported smaller soil lead elevations in the vicinity of eighteen brick veneer houses in Detroit. Soil lead levels near painted barns located in rural areas were similar to urban soil lead concentrations near painted houses, suggesting the importance of leaded paint at both urban and rural locations. The baseline lead concentration for household dust of 300 μg/g was increased to 2000 μg/g for houses with interior lead based paints. The additional 1700 μg/g would add 85 μg Pb/day to the potential exposure of a child (Table 7-25). This increase would occur in an urban or nonurban environment and would be in addition to the urban residential increase if the lead-based painted house were in an urban environment.

7.3.2.1.3 Family gardens. Several studies have shown potentially higher lead exposure through the consumption of home-grown produce from family gardens grown on high lead soils or near sources of atmospheric lead. Kneip (1978) found elevated levels of lead in leafy vegetables, root crops, and garden fruits associated qualitatively with traffic density and soil lead. Spittler and Feder (1978) reported a linear correlation between soil lead (100 to 1650 μg/g) and leafy or root vegetables. Preer et al. (1980) found a three-fold increase in lead concentrations of leafy vegetables (from 6 to 16 μg/g) in the soil lead range from 150 to 2200 μg/g. In none of these studies were the lowest soil lead concentrations in the normal range of 10 to 25 μg/g, nor were any lead concentrations reported for vegetables as low as those of Wolnik et al. (1983) (see Table 7-9).

In family gardens, lead may reach the edible portions of vegetables by deposition of atmospheric lead directly on aboveground plant parts or on soil, or by the flaking of lead-containing paint chips from houses. Traffic density and distance from the road are not good predictors of soil or vegetable lead concentrations (Preer et al., 1980). Air concentrations and particle size distributions are the important determinants of deposition on soil or vegetation surfaces. Even at relatively high air concentrations (1.5 $\mu g/m^3$) and deposition velocity (0.5 cm/sec) (see Section 6.4.1), it is unlikely that surface deposition alone can account for more than 2-5 μg/g lead on the surface of lettuce during a 21-day growing period. It appears that a significant fraction of the lead in both leafy and root vegetables derives from the soil.

Using the same air concentration and deposition velocity values, a maximum of 1000 μg lead has been added to each cm^2 of the surface of the soil over the past 40 years. With cultivation to a depth of 15 cm, it is not likely that atmospheric lead alone can account for more than a few hundred μg/g of soil in urban gardens. Urban soils with lead concentrations of 500 μg/g or more must certainly have another source of lead. In the absence of a nearby (<5 km) stationary industrial source, paint chips seem the most likely explanation. Even if the house no longer stands at the site, the lead from paint chips may still be present in the soil.

TABLE 7-25. SUMMARY OF POTENTIAL ADDITIVE EXPOSURES TO LEAD

	Total lead consumed (µg/day)	Atmospheric lead consumed (µg/day)	Other lead sources (µg/day)
Baseline exposure:			
Child			
Inhaled air	0.5	0.5	-
Food, water & beverages	39.9	12.1	27.8
Dust	21.0	19.0	2.0
Total baseline	61.4	31.6	29.8
Additional exposure due to:			
Urban atmospheres[1]	99	98	
Family gardens[2]	800	200	600
Interior lead paint[3]	85		85
Residence near smelter[4]	1300	1300	
Secondary occupational[5]	150		
Baseline exposure:			
Adult male			
Inhaled air	1.0	1.0	-
Food, water & beverages	70.8	20.2	50.6
Dust	4.5	2.9	1.6
Total baseline	76.3	24.1	52.2
Additonal exposure due to:			
Urban atmospheres[1]	28	28	
Family gardens[2]	2000	500	1500
Interior lead paint[3]	17		17
Residence near smelter[4]	370	370	
Occupational[6]	1100	1100	
Secondary occupational[5]	21		
Smoking	30	27	3
Wine consumption	100	?	?

[1]includes lead from household and street dust (1000 µg/g) and inhaled air (.75 µg/m^3).
[2]assumes soil lead concentration of 2000 µg/g; all fresh leafy and root vegetables, sweet corn of Table 7-13 replaced by produce from garden. Also assumes 25% of soil lead is of atmospheric origin.
[3]assumes household dust rises from 300 to 2000 µg/g. Dust consumption remains the same as baseline.
[4]assumes household and street dust increases to 25,000 µg/g.
[5]assumes household dust increases to 2400 µg/g.
[6]assumes 8 hr shift at 10 µg Pb/m^3 or 90% efficiency of respirators at 100 µg Pb/m^3, and occupational dusts at 100,000 µg/m^3.

Studies of family gardens do not agree on the concentrations of lead in produce. At the higher soil concentrations, Kneip (1978) reported 0.2 to 1 μg/g in vegetables, Spittler and Feder (1978) reported 15 to 90 μg/g, and Preer et al. (1980) found 2 to 16 μg/g. Since the Spittler and Feder (1978) and Preer et al. (1980) studies dealt with soils in the range of 2000 μg/g, these data can be used to calculate a worst case exposure of lead from family gardens. Assuming 15 μg/g for the leafy and root vegetables [compared to 0.01 to 0.05 μg/g of the Wolnik et al. (1983) study] family gardens could add 2000 μg/day if the 137 g of leafy and root vegetables, sweet corn and potatoes consumed by adult males (Table 7-13) were replaced by family garden products. Comparable values for children and adult females would be 800 and 1600 μg/day, respectively. No conclusive data are available for vine vegetables, but the ranges of 0.08 to 2 μg/g for tomatoes suggest that the contamination by lead from soil is much less for vine vegetables than for leafy or root vegetables.

7.3.2.1.4 Houses with lead plumbing. The Glasgow Duplicate Diet Study (United Kingdom Department of the Environment, 1982) reports that children approximately 13 weeks old living in houses with lead plumbing consume 6 to 480 μg Pb/day. Water lead levels in the 131 homes studied ranged from less than 50 to over 500 μg/l. Those children and mothers living in the homes containing high water-lead levels generally had greater total lead consumption and higher blood lead levels, according to the study. Breast-fed infants were exposed to much less lead than bottle-fed infants. Because the project was designed to investigate child and mother blood lead levels over a wide range of water lead concentrations, the individuals studied do not represent a typical cross-section of the population. However, results of the study suggest that infants living in homes with lead plumbing may have exposure to considerable amounts of lead. This conclusion was also demonstrated by Sherlock et al. (1982) in a duplicate diet study in Ayr, Scotland.

7.3.2.1.5 Residences near smelters and refineries. Air concentrations within 2 km of lead smelters and refineries average 5 to 15 $\mu g/m^3$. Assuming the same indoor/outdoor ratio of atmospheric lead for nonurban residents (0.5), residents near smelters would be exposed to inhaled air lead concentrations of about 6 $\mu g/m^3$, compared to 0.05 $\mu g/m^3$ for the background levels. Household dust concentrations range from 3000 to 100,000 μg/g (Landrigan et al., 1975). A value of 25,000 μg/g is assumed for household dust near a smelter. Between inhaled air and dust, a child in this circumstance would be exposed to 1300 μg Pb/day above background levels. Exposures for adults would be much less, since they consume only 20 percent of the dusts children consume.

7.3.2.1.6 Occupational exposures. The highest and most prolonged exposures to lead are found among workers in the lead smelting, refining, and manufacturing industries (World Health Organization, 1977). In all work areas, the major route of lead exposure is by inhalation and

ingestion of lead-bearing dusts and fumes. Airborne dusts settle out of the air onto food, water, the workers' clothing, and other objects, and may be transferred subsequently to the mouth. Therefore, good housekeeping and good ventilation have a major impact on exposure. It has been found that levels might be quite high in one factory and low in another solely because of differences in ventilation, or differences in custodial practices and worker education. The estimate of additional exposure on Table 7-25 is for an 8 hour shift at 100 μg Pb/m^3. Occupational exposure under these conditions is primarily determined by occupational dust consumed. Even tiny amounts (e.g., 10 mg) of dust containing 100,000 μg Pb/g dust can account for 1,000 μg/day exposure.

7.3.2.1.6.1 Lead mining, smelting, and refining. Roy (1977) studied exposures during mining and grinding of lead sulfide at a mill in the Missouri lead belt. Primary smelting operations were 2.5 miles from the mill, hence the influence of the smelter was believed to be negligible. The total airborne lead levels were much greater than the concentrations of respirable lead, indicating a predominance of coarse material.

The greatest potential for high-level exposure exists in the process of lead smelting and refining (World Health Organization, 1977). The most hazardous operations are those in which molten lead and lead alloys are brought to high temperatures, resulting in the vaporization of lead. This is because condensed lead vapor or fume has, to a substantial degree, a small (respirable) particle size range. Although the total air lead concentration may be greater in the vicinity of ore-proportioning bins than it is in the vicinity of a blast furnace in a smelter, the amount of particle mass in the respirable size range may be much greater near the furnace.

A measure of the potential lead exposure in smelters was obtained in a study of three typical installations in Utah (World Health Organization, 1977). Air lead concentrations near all major operations, as determined using personal monitors worn by workers, were found to vary from about 100 to more than 4000 $\mu g/m^3$. Obviously, the hazard to these workers would be extremely serious if it were not for the fact that the use of respirators is mandatory in these particular smelters. Maximum airborne lead concentrations of about 300 $\mu g/m^3$ were measured in a primary lead-zinc smelter in the United Kingdom (King et al., 1979). These authors found poor correlations between airborne lead and blood lead in the smelter workers, and concluded that a program designed to protect these workers should focus on monitoring of biological parameters rather than environmental levels.

Spivey et al. (1979) studied a secondary smelter in southern California which recovers lead mainly from automotive storage batteries. Airborne lead concentrations of 10 to 4800 $\mu g/m^3$ were measured. The project also involved measurement of biological parameters as well as a survey of symptoms commonly associated with lead exposure; a poor correlation was found

between indices of lead absorption and symptom reporting. The authors suggested that such factors as educational level, knowledge of possible symptoms, and biological susceptibility may be important factors in influencing symptom reporting. In a second article covering this same study, Brown et al. (1980) reported that smokers working at a smelter had greater blood lead levels than nonsmokers. Furthermore, smokers who brought their cigarettes into the workplace had greater blood lead levels than those who left their cigarettes elsewhere. It was concluded that direct environmental contamination of the cigarettes by lead-containing dust may be a major exposure pathway for these individuals (See Section 7.3.2.3.1).

Secondary lead smelters in Memphis, Tennessee and Salt Lake City, Utah were studied by Baker et al. (1979). The former plant extracted lead principally from automotive batteries, producing 11,500 metric tons of lead in the eleven months preceding the measurements. The latter plant used scrap to recover 258 metric tons of lead in the six months preceding the measurements. Airborne concentrations of lead in the Tennessee study exceeded 200 $\mu g/m^3$ in some instances, with personal air sampler data ranging from 120 $\mu g/m^3$ for a battery wrecker to 350 $\mu g/m^3$ for two yard workers. At the Utah plant, airborne lead levels in the office, lunchroom, and furnace room (furnace not operating) were 60, 90, and 100 $\mu g/m^3$, respectively. When charging the furnace, the last value increased to 2650 $\mu g/m^3$. Personal samplers yielded concentrations of 17 $\mu g/m^3$ for an office worker, 700 $\mu g/m^3$ for two welders, and 2660 $\mu g/m^3$ for two furnace workers. Some workers in both plants showed clinical manifestations of lead poisoning; a significant correlation was found between blood lead levels and symptom reporting.

High levels of atmospheric lead are also found in foundries in which molten lead is alloyed with other metals. Berg and Zenz (1967) found in one such operation that average concentrations of lead in various work areas were 280 to 600 $\mu g/m^3$. These levels were subsequently reduced to 30 to 40 $\mu g/m^3$ with the installation of forced ventilation systems to exhaust the work area atmosphere to the outside.

7.3.2.1.6.2 Welding and cutting of metals containing lead. When metals that contain lead or are protected with a lead-containing coating are heated in the process of welding or cutting, copious quantities of lead in the respirable size range may be emitted. Under conditions of poor ventilation, electric arc welding of zinc silicate-coated steel (containing 4.5 mg Pb/cm^2 of coating) produced breathing-zone concentrations of lead reaching 15,000 $\mu g/m^3$, far in excess of 450 $\mu g/m^3$, which is the current occupational short-term exposure limit (STEL) in the United States (Pegues, 1960). Under good ventilation conditions, a concentration of 140 $\mu g/m^3$ was measured (Tabershaw et al., 1943).

In a study of salvage workers using oxyacetylene cutting torches on lead-painted structural steel under conditions of good ventilation, breathing-zone concentrations of lead averaged 1200 $\mu g/m^3$ and ranged as high as 2400 $\mu g/m^3$ (Rieke, 1969). Lead poisoning in workers

dismantling a painted bridge has been reported by Graben et al. (1978). Fischbein et al. (1978) discuss the exposure of workers dismantling an elevated subway line in New York City, where the lead content of the paint is as great as 40 percent. The authors report that one mm^3 of air can contain 0.05 g lead at the source of emission. Similarly, Grandjean and Kon (1981) report elevated lead exposures of welders and other employees in a Baltimore, Maryland shipyard.

7.3.2.1.6.3 Storage battery industry. At all stages in battery manufacture except for final assembly and finishing, workers are exposed to high air lead concentrations, particularly lead oxide dust. For example, Boscolo et al. (1978) report air lead concentrations of 16-100 $\mu g/m^3$ in a battery factory in Italy, while values up to 1315 $\mu g/m^3$ have been measured by Richter et al. (1979) in an Israeli battery factory. Excessive concentrations, as great as 5400 $\mu g/m^3$, have been reported by the World Health Organization (1977).

7.3.2.1.6.4 Printing industry. The use of lead in typesetting machines has declined in recent years. Air concentrations of 10 to 30 $\mu g/m^3$ have been reported where this technique is used (Parikh et al., 1979). Lead is also a component of inks and dyes used in the printing industry, and consequently can present a hazard to workers handling these products.

7.3.2.1.6.5 Alkyl lead manufacture. Workers involved in the manufacture of alkyl lead compounds are exposed to both inorganic and alkyl lead. Some exposure also occurs at the petroleum refineries where the two compounds are blended into gasoline, but no data are available on these blenders.

The major potential hazard in the manufacture of tetraethyl lead and tetramethyl lead is from skin absorption, which is minimized by the use of protective clothing. Linch et al. (1970) found a correlation between an index of organic plus inorganic lead concentrations in a plant and the rate of lead excretion in the urine of workers. Significant concentrations of organic lead in the urine were found in workers involved with both tetramethyl lead and tetraethyl lead; lead levels in the tetramethyl lead workers were slightly higher because the reaction between the organic reagent and lead alloy takes place at a somewhat higher temperature and pressure than that employed in tetraethyl lead production.

Cope et al. (1979) used personal air samplers to assess exposures of five alkyl lead workers exposed primarily to tetraethyl lead. Blood and urine levels were measured over a six-week period. Alkyl lead levels ranged from 1.3 to 1249 $\mu g/m^3$, while inorganic lead varied from 1.3 to 62.6 $\mu g/m^3$. There was no significant correlation between airborne lead (either alkyl or inorganic) and blood or urine levels. The authors concluded that biological monitoring, rather than airborne lead monitoring, is a more reliable indicator of potential exposure problems.

7.3.2.1.6.6 Other occupations. In both the rubber products industry and the plastics industry there are potentially high exposures to lead. The potential hazard of the use of lead stearate as a stabilizer in the manufacture of polyvinyl chloride was noted in the 1971 Annual Report of the British Chief Inspector of Factories (United Kingdom Department of Employment, Chief Inspector of Factories 1972). The inspector stated that the number of reported cases of lead poisoning in the plastics industry was second only to that in the lead smelting industry. Scarlato et al. (1969) reported other individual cases of exposure. The source of this problem is the dust that is generated when the lead stearate is milled and mixed with the polyvinyl chloride and the plasticizer. An encapsulated stabilizer which greatly reduces the occupational hazard is reported by Fischbein et al. (1982).

Sakurai et al. (1974), in a study of bioindicators of lead exposure, found ambient air concentrations averaging 58 $\mu g/m^3$ in the lead-covering department of a rubber hose manufacturing plant. Unfortunately, no ambient air measurements were taken for other departments or the control group.

The manufacture of cans with leaded seams may expose workers to elevated ambient lead levels. Bishop (1980) reports airborne lead concentrations of 25 to 800 $\mu g/m^3$ in several can manufacturing plants in the United Kingdom. Between 23 and 54 percent of the airborne lead was associated with respirable particles, based on cyclone sampler data.

Firing ranges may be characterized by high airborne lead concentrations, hence instructors who spend considerable amounts of time in such areas may be exposed to lead. For example, Smith (1976) reports airborne lead concentrations of 30 to 160 μ/m^3 at a firing range in the United Kingdom. Anderson et al. (1977) discuss lead poisoning in a 17 year old male employee of a New York City firing range, where airborne lead concentrations as great as 1000 $\mu g/m^3$ were measured during sweeping operations. Another report from the same research group presents time-weighted average exposures of instructors of 45 to 900 $\mu g/m^3$ in three New York City firing ranges (Fischbein et al., 1979).

Removal of leaded paint from walls and other surfaces in old houses may pose a health hazard. Feldman (1978) reports an airborne lead concentration of 510 $\mu g/m^3$, after 22 minutes of sanding an outdoor post coated with paint containing 2.5 mg Pb/cm^2. After only five minutes of sanding an indoor window sill containing 0.8 to 0.9 mg Pb/cm^2, the air contained 550 $\mu g/m^3$. Homeowners who attempt to remove leaded paint themselves may be at risk of excessive lead exposure. Garage mechanics may be exposed to excessive lead concentrations. Clausen and Rastogi (1977) report airborne lead levels of 0.2 to 35.5 $\mu g/m^3$ in ten garages in Denmark; the greatest concentration was measured in a paint workshop. Used motor oils were found to contain 1500 to 3500 µg Pb/g, while one brand of unused gear oil contained 9280 µg Pb/g. The

authors state that absorption through damaged skin could be an important exposure pathway. Other occupations involving risk of lead exposure include stained glass manufacturing and repair, arts and crafts, and soldering and splicing.

7.3.2.1.7 Secondary occupational exposure. Winegar et al. (1977) examined environmental concentrations as well as biological indicators and symptom reporting in workers in a secondary lead smelter near St. Paul, Minnesota. The smelter recovers approximately 9000 metric tons of lead per year from automotive batteries. The lead concentrations in cuff dust from trousers worn by two workers were 60,000 and 600,000 μg/g. The amount of lead contained in pieces of cloth 1 cm^2 cut from the bottoms of trousers worn by the workers ranged from 110 to 3000 μg, with a median of 410 μg. In all cases, the trousers were worn under coveralls. Dust samples from 25 households of smelter workers ranged from 120 to 26,000 μg/g, with a median of 2400 μg/g. No significant correlations were found between dust lead concentrations and biological indicators, or between symptom reporting and biological indicators. However, there was an increased frequency of certain objective physical signs, possibly due to lead toxicity, with increased blood lead level. The authors also concluded that the high dust lead levels in the workers' homes are most likely due to lead originating in the smelter.

7.3.2.2 Additive Exposure Due to Age, Sex, or Socio-Economic Status.

7.3.2.2.1 Quality and quantity of food. The quantity of food consumed per body weight varies greatly with age and somewhat with sex. A 14 kg, 2-year-old child eats and drinks 1.5 kg food and water per day. This is 110 g/kg, or 3 times the consumption of an 80 kg adult male, who eats 39 g/kg. Teenage girls consume less than boys and elderly women eat more than men, on a body weight basis.

It is likely that poor people eat less frozen and pre-prepared foods, more canned foods. Rural populations probably eat more home-grown foods and meats packed locally.

7.3.2.2.2 Mouthing behavior of children. Children place their mouths on dust collecting surfaces and lick non-food items with their tongues. This fingersucking and mouthing activity are natural forms of behavior for young children which expose them to some of the highest concentrations of lead in their environment. A single gram of dust may contain ten times more lead than the total diet of the child.

7.3.2.3 Special Habits or Activities.

7.3.2.3.1 Smoking. Lead is also present in tobacco. The World Health Organization (1977) estimates a lead content of 2.5 to 12.2 μg per cigarette; roughly two to six percent of this lead may be inhaled by the smoker. The National Academy of Sciences (1980) has used these data to conclude that a typical urban resident who smokes 30 cigarettes per day may inhale roughly equal amounts of lead from smoking and from breathing urban air.

7.3.2.3.2 Alcoholic beverages. Reports of lead in European wines (Olsen et al., 1981; Boudene et al., 1975; Zurlo and Graffini, 1973) show concentrations averaging 100 to 200 µg/l and ranging as high as 300 µg/l. Measurements of lead in domestic wines were in the range of 100 to 300 µg/l for California wines with and without lead foil caps. The U.S. Food and Drug Administration (1983) found 30 µg/l in the 1982 Market Basket Survey. The average adult consumption of table wine in the U.S. is about 12 g. Even with a lead content of 0.1 µg/g, which is ten times higher than drinking water, wine does not appear to represent a significant potential exposure to lead. At one 1/day, however, lead consumption would be greater than the total baseline consumption.

McDonald (1981) points out that older wines with lead foil caps may represent a hazard, especially if they have been damaged or corroded. Wai et al. (1979) found that the lead content of wine rose from 200 to 1200 µg/l when the wine was allowed to pass over the thin ring of residue left by the corroded lead foil cap. Newer wines (1971 and later) use other means of sealing. If a lead foil is used, the foil is tin-plated and coated with an acid-resistant substance. Lead levels in beer are generally smaller than those in wine; Thalacker (1980) reports a maximum concentration of 80 µg/l in several brands of German beer. The U.S. Food and Drug Administration (1983) found 13 µg/l in beer consumed by Americans.

7.3.2.3.3 Pica. Pica is the compulsive, habitual consumption of non-food items, such as paint chips and soil. This habit can present a significant lead exposure to the afflicted person, especially to children, who are more apt to have pica. There are very little data on the amounts of paint or soil eaten by children with varying degrees of pica. Exposure can only be expressed on a unit basis. Billick and Gray (1978) report lead concentrations of 1000 to 5000 µg/cm^2 in lead-based paint pigments. A single chip of paint can represent greater exposure than any other source of lead to a child who has pica. A gram of urban soil may have 150 to 2000 µg lead.

7.3.2.3.4 Glazed earthenware vessels. Another potential source of dietary lead poisoning is the use of inadequately glazed earthenware vessels for food storage and cooking. An example of this danger involved the severe poisoning of a family in Idaho which resulted from drinking orange juice that had been stored in an earthenware pitcher (Block, 1969). Similar cases, sometimes including fatalities, have involved other relatively acidic beverages such as fruit juices and soft drinks, and have been documented by other workers (Klein et al., 1970; Harris and Elsen, 1967). Because of these incidents, the U.S. Food and Drug Administration (1979) has established a maximum permissible concentration of 7 µg Pb/g in solution after leaching with 4 percent acetic acid in the earthenware vessel for 24 hours.

Inadequately glazed pottery manufactured in other countries continues to pose a significant health hazard. For example, Spielholtz and Kaplan (1980) report 24 hour acetic acid-leached lead concentrations as great as 4400 µg/g in Mexican pottery. The leached lead

decreased with exposure time, and after several days appears to asymptotically approach a value which may be as great as 600 µg/g. These investigators have also measured excessive lead concentrations leached into acidic foods cooked for two hours in the same pottery. Similarly, Acra et al. (1981) report that 85 percent of 275 earthenware vessels produced in primitive Lebanese potteries had lead levels above the 7 µg/g limit set by the U.S. FDA. However, only 9 percent of 75 vessels produced in a modern Beirut pottery exceeded the limit. Cubbon et al. (1981) have examined properly glazed ceramic plates in the United Kingdom, and have found a decrease in leached lead with exposure time down to very low levels. The authors state that earthenware satisfying the 7 µg/g limit will contribute about 3 µg/day to the dietary intake of the average consumer.

7.3.2.3.5 Hobbies. There are a few hobbies where the use of metallic lead or solder may present a hazard to the user. Examples are electronics projects, stained glass window construction, and firing range ammunition recovery. There are no reports in which the exposure to lead has been quantified during these activities.

7.3.3 Summary of Additive Exposure Factors

Beyond the baseline level of human exposure, additional amounts of lead consumption are largely a matter of individual choice or circumstance. Many of these additional exposures arise from the ingestion of atmospheric lead in dust. In one or more ways probably 90 percent of the American population are exposed to lead at greater than baseline levels. A summary of the most common additive exposure factors appears on Table 7-25. In some cases, the additive exposure can be fully quantified and the amount of lead consumed can be added to the baseline consumption. These may be continuous (urban residence), or seasonal (family gardening) exposures. Some factors can be quantified only on a unit basis because of wide ranges in exposure duration or concentration. For example, factors affecting occupational exposure are air lead concentrations (10 to 4000 µg/m^3), use and efficiency of respirators, length of time of exposure, dust control techniques, and worker training in occupational hygiene.

7.4 SUMMARY

Ambient airborne lead concentrations have shown no marked trend from 1965 to 1977. Over the past five years, however, distinct decreases have occurred. The mean urban air concentrations has dropped from 0.91 µg/m^3 in 1977 to 0.32 µg/m^3 in 1980. These decreases reflect the smaller lead emissions from mobile sources in recent years. Airborne size distribution data indicate that most of the airborne lead mass is found in submicron particles.

Atmospheric lead is deposited on vegetation and soil surfaces, entering the human food chain through contamination of grains and leafy vegetables, of pasture lands, and of soil moisture taken up by all crops. Lead contamination of drinking water supplies appears to originate mostly from within the distribution system.

Most people receive the largest portion of their lead intake through foods. Unprocessed foods such as fresh fruits and vegetables receive lead by atmospheric deposition as well as uptake from soil; crops grown near heavily traveled roads generally have greater lead levels than those grown at greater distances from traffic. For many crops the edible internal portions of the plant (e.g., kernels of corn and wheat) have considerably less lead than the outer, more exposed parts such as stems, leaves, and husks. Atmospheric lead accounts for about 30 percent of the total adult lead exposure, and 50 percent of the exposure for children. Processed foods have greater lead concentrations than unprocessed foods, due to lead inadvertently added during processing. Foods packaged in soldered cans have much greater lead levels than foods packaged in other types of containers. About 45 percent of the baseline adult exposure to lead results from the use of solder lead in packaging food and distributing drinking water.

Significant amounts of lead in drinking water can result from contamination at the water source and from the use of lead solder in the water distribution system. Atmospheric deposition has been shown to increase lead in rivers, reservoirs, and other sources of drinking water; in some areas, however, lead pipes pose a more serious problem. Soft, acidic water in homes with lead plumbing may have excessive lead concentrations. Besides direct consumption of the water, exposure may occur when vegetables and other foods are cooked in water containing lead.

All of the categories of potential lead exposure discussed above may influence or be influenced by dust and soil. For example, lead in street dust is derived primarily from vehicular emissions, while leaded house dust may originate from nearby stationary or mobile sources. Food and water may include lead adsorbed from soil as well as deposited atmospheric material. Flaking leadbased paint has been shown to increase soil lead levels. Natural concentrations of lead in soil average approximately 15 µg/g; this natural lead, in addition to anthropogenic lead emissions, influences human exposure.

Americans living in rural areas away from sources of atmospheric lead consume 50 to 75 µg Pb/day from all sources. Circumstances which can increase this exposure are: urban residence (25 to 100 µg/day), family garden on high-lead soil (800 to 2000 µg/day), houses with interior lead-based paint (20 to 85 µg/day), and residence near a smelter (400 to 1300 µg/day). Occupational settings, smoking, and wine consumption also can increase consumption of lead according to the degree of exposure.

A number of manmade materials are known to contain lead, the most important being paint and plastics. Lead-based paints, although no longer used, are a major problem in older homes. Small children who ingest paint flakes can receive excessive lead exposure. Incineration of plastics may emit large amounts of lead into the atmosphere. Because of the increasing use of plastics, this source is likely to become more important. Other manmade materials containing lead include colored dyes, cosmetic products, candle wicks, and products made of pewter and silver.

The greatest occupational exposures are found in the lead smelting and refining industries. Excessive airborne lead concentrations and dust lead levels are occasionally found in primary and secondary smelters; smaller exposures are associated with mining and processing of the lead ores. Welding and cutting of metal surfaces coated with lead-based paint may also result in excessive exposure. Other occupations with potentially high exposures to lead include the manufacture of lead storage batteries, printing equipment, alkyl lead, rubber products, plastics, and cans; individuals removing lead paint from walls and those who work in indoor firing ranges may also be exposed to lead.

Environmental contamination by lead should be measured in terms of the total amount of lead emitted to the biosphere. American industry contributes several hundred thousand tons of lead to the environment each year: 35,000 tons from petroleum additives, 50,000 tons from ammunition, 45,000 tons in glass and ceramic products, 16,000 tons in paint pigments, 8,000 tons in food can solder, and untold thousands of tons of captured wastes during smelting, refining, and coal combustion. These are uses of lead which are generally not recoverable, thus they represent a permanent contamination of the human or natural environment. Although much of this lead is confined to municipal and industrial waste dumps, a large amount is emitted to the atmosphere, waterways, and soil, to become a part of the biosphere.

Potential human exposure can be expressed as the concentrations of lead in these environmental components (air, dust, food, and water) that interface with man. It appears that, with the exception of extraordinary cases of exposure, about 100 μg of lead are consumed daily by each American. This amounts to only 8 tons for the total population, or less than 0.01 percent of the total environmental contamination.

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APPENDIX 7A
SUPPLEMENTAL AIR MONITORING INFORMATION

7A.1 AIRBORNE LEAD SIZE DISTRIBUTION

In Section 7.2.1.3.1, several studies of the particle size distributions for atmospheric lead were discussed. The distributions at forty locations were given in Figure 7-5. Supplementary information from each of these studies is given in Table 7A-1.

7A.2 NONURBAN AIR MONITORING INFORMATION

Section 7.2.1.1.1 describes ambient air lead concentrations in the United States, emphasizing monitoring network data from urban stations. Table 7-2 gives the cumulative frequency distributions of quarterly averages for urban stations. Comparable data for nonurban stations are given in Table 7A-2. The trends shown by the two tables are similar, but the numbers of reports for nonurban stations has decreased markedly since 1977. Table 7A-2 does not include nonurban stations located near specific point sources. The detection limit has decreased over the years, thus there are fewer reports of air concentrations below the detection limit since 1975.

The distributions of annual averages among specific concentration intervals are given in Table 7A-3 for nonurban stations. Comparable data were presented graphically in Figure 7-2 for urban stations.

TABLE 7A-1. INFORMATION ASSOCIATED WITH THE AIRBORNE LEAD SIZE DISTRIBUTIONS OF FIGURE 7-5

Graph no.	Reference	Dates of sampling	Location of sampling	Type of sampler	C_T µg/m³	Approx. MMD µm
1	Lee et al. (1972)	Jan. - Dec. 1970 Average of 4 quarterly composited samples, representing a total of 21 sampling periods of 24 hours each	Chicago, Illinois	Modified Anderson impactor with backup filter	3.2	0.68
2	Lee et al. (1972)	Mar. - Dec. 1970 Same averaging as Graph 1, total of 18 sampling periods	Cincinnati, Ohio	Modified Andersen impactor with backup filter	1.8	0.48
3	Lee et al. (1972)	Jan. - Dec. 1970 Same averaging as Graph 1, total of 21 sampling periods	Denver, Colorado	Modified Andersen impactor with backup filter	1.8	0.50
4	Lee et al. (1972)	Mar. - Dec. 1970 Same averaging as Graph 1, total of 20 sampline periods	Philadelphia, Pennsylvania	Modified Andersen impactor with backup filter	1.6	0.47
5	Lee et al. (1972)	Jan. - Dec. 1970 Same averaging as Graph 1, total of 22 sampling periods	St. Louis, Missouri	Modified Andersen impactor with backup filter	1.8	0.69
6	Lee et al. (1972)	Jan. - Dec. 1970 Same averaging as Graph 1, total of 23 sampling periods	Washington, D.C.	Modified Andersen impactor with backup filter	1.3	0.42

TABLE 7A-1. (continued)

Graph no	Reference	Dates of sampling	Location of sampling	Type of sampler	C_T µg/m³	Approx. MMD µm
7	Lee et al. (1968)	September 1966 Average of 14 runs, 24 hours each	Cincinnati, Ohio	Andersen impactor with backup filter, 1.2m above the ground	2.8	0.29
8	Lee et al. (1968)	February 1967 Average of 3 runs 4 days each	Fairfax, Ohio suburb of Cincinnati	Andersen impactor with backup filter, 1.2m above the ground	0.69	0.42
9	Peden (1977)	Summer 1975 Average of 4 runs, average 8 days each	Alton, Illinois, industrial area near St. Louis	Andersen impactor no backup filter	0.24	2.1
10	Peden (1977)	Summer 1972 Average of 3 runs, average 10 days each	Centreville, Illinois, downwind of a zinc smelter	Andersen impactor with backup filter	0.62	0.41
11	Peden (1977)	Summer 1973 Average of 2 runs average 5 days each	Collinsville, Illinois industrial area near St. Louis	Andersen impactor with backup filter	0.67	0.24
12	Peden (1977)	Summer 1973 Average of 2 runs, average 6 days each	KMOX radio transmitter, Illinois, industrial area near St. Louis	Andersen impactor with backup filter	0.60	0.31
13	Peden (1977)	Summer 1972 Average of 9 runs, average 9 days each	Pere Marquette State Park, Illionis, upwind of St. Louis	Andersen impactor with backup filter	0.15	0.51
14	Peden (1977)	Summer 1975 Average of 4 runs, average 8 days each	Wood River, Illinois, industrial area near St. Louis	Andersen impactor, no backup filter	0.27	1.8

TABLE 7A-1 (continued)

Graph no	Reference	Dates of sampling	Location of sampling	Type of sampler	C_T µg/m³	Approx. MMD µm
15	Cholak et al. (1968)	April 1968 average of several runs, 3 days each	3 sites: 10,400 and 3300m from Interstate 75, Cincinnati, Ohio	Andersen impactor with backup filter	7.8* 1.7 1.1	0.32
16	McDonald and Duncan (1979)	June 1975 One run of 15 days	Glasgow, Scotland	Casella impactor with backup filter, 30m above the ground	0.53	0.51
17	Dorn et al. (1976)	Winter, spring, summer 1972 Average of 3 runs, 27 days each	Southeast Missouri, 800m from a lead smelter	Andersen impactor, no backup filter, 1.7m above the ground	1.0	3.8
18	Dorn et al. (1976)	Winter, spring, summer 1972 Average of 3 runs, 14 days each	Southeast Missouri, 75 km from the lead smelter of Graph 17	Andersen impactor, no backup filter, 1.7m above the ground	0.11	2.4
19	Daines et al. (1970)	1968 Average of continuous 1-week runs over an 8-month period	3 sites: 9, 76, and 530m from U.S. Route 1, New Brunswick, New Jersey	Cascade impactor with backup filter	4.5 2.2 1.5	0.35
20	Martens et al. (1973)	July 1971 One run of 4 days	9 sites throughout San Francisco area	Andersen impactor with backup filter	0.84	0.49
21	Lundgren (1970)	November 1968 Average of 10 runs, 16 hours each	Riverside, California	Lundgren impactor	0.59	0.50
22	Huntzicker et al. (1975)	May 1973 One run of 8 hours	Shoulder of Pasadena Freeway near downtown Los Angeles, California	Andersen impactor with backup filter, 2m above the ground	14.0	0.32

TABLE 7A-1 (continued)

Graph no	Reference	Dates of sampling	Location of sampling	Type of sampler	C_T µg/m³	Approx. MMD µm
23	Huntzicker et al. (1975)	Februray 1974 One run of 6 days	Pasadena, California	Andersen impactor with backup filter, on roof of 4 story building	3.5	0.72
24	Davidson (1977)	May and July 1975 Average of 2 runs, 61 hours each	Pasadena, California	Modified Andersen impactor with backup filter on roof of 4 story building	1.2	0.97
25	Davidson et al. (1980)	October 1979 One run of 120 hours	Clingman's Dome Great Smokies National Park, elev. 2024m	2 Modified Andersen impactors with backup filters, 1.2m above the ground	0.014	1.0
26	Davidson et al. (1981a)	July-Sep. 1979 Average of 2 runs, 90 hours each	Pittsburgh, Pennsylvania	Modified Andersen impactor with backup filter, 4m above the ground	0.60	0.56
27	Davidson et al. (1981b)	December 1979 One run of 52 hours	Nepal Himalayas elev. 3962m	Modified Andersen impactor with backup filter, 1.2m above the ground	0.0014	0.54
28	Gould and Davidson (1982)	June 1980 One run of 72 hours	Export, Pennsylvania rural site 40 km east of Pittsburgh	2 Modified Andersen impactors with backup filters, 1.2m above the ground	0.111	1.2
29	Gould and Davidson (1982)	July 1980 One run of 34 hours	Packwood, Washington rural site in Gifford Pinchot National Forest	Modified Andersen impactor with backup filter, 1.5m above the ground	0.016	0.40

TABLE 7A-1 (continued)

Graph no	Reference	Dates of sampling	Location of sampling	Type of sampler	C T µg/m³	Approx. MMD µm
30	Goold and Davidson (1982)	July-Aug. 1980 One run of 92 hours	Hurricane Ridge Olympic National Park elev. 1600m	Modified Andersen impactor with backup filter, 1.5m above the ground	0.0024	0.87
31	Duce et al. (1976)	May - June 1975 One run of 112 hours	Southeast coast of Bermuda	Sierra high-volume impactor with backup filter, 20m above the ground	0.0085	0.57
32	Duce et al. (1976)	July 1975 One run of 79 hours	Southeast coast of Bermuda	Sierra high-volume impactor with backup filter, 20m above the ground	0.0041	0.43
33	Harrison et al. (1971)	April 1968 Average of 21 runs, 2 hours each	Ann Arbor, Michigan	Modified Andersen impactor with backup filter, 20m above the ground	1.8	0.16
34	Gillette and Winchester (1972)	Oct. 1968 Average of 15 runs, 24 hours each	Ann Arbor, Michigan	Andersen impactor with backup filter	0.82	0.28
35	Gillette and Winchester (1972)	May - Sept. 1968 Average of 10 runs, 8 hours each	Chicago, Illinois	Andersen impactor with backup filter	1.9	0.39
36	Gillette and Winchester (1972)	Oct. 1968 Average of 3 runs, 24 hours each	Lincoln, Nebraska	Andersen impactor with backup filter	0.14	0.42
37	Johansson et al. (1976)	June - July 1973 Average of 15 runs, average 50 hr each	2 sites in Tallahassee, Florida	Delron Battelle-type impactor, no backup filter, on building roofs	0.24	0.62

TABLE 7A-1 (continued)

Graph no	Reference	Dates of sampling	Location of sampling	Type of sampler	C_T µg/m³	Approx. MMD µm
38	Cawse et al. (1974)	July - Dec. 1973	Chilton, England	Andersen impactor with backup filter, 1.5m above the ground	0.16	0.57
39	Pattenden et al. (1974)	May - Aug. 1973 Average of 4 runs, 1 month each	Trebanos, England	Andersen impactor with backup filter, 1.5m above the ground	0.23	0.74
40	Bernstein and Rahn (1979)	Aug. 1976 Average of 4 runs, 1 week each	New York City	Cyclone sampling system with backup filter, on roof on 15 story building	1.2	0.64

[a]Airborne concentrations for filters run at the same sites as the impactor, but during different time periods. Impactor concentrations not available.

TABLE 7A-2. CUMULATIVE FREQUENCY DISTRIBUTIONS OF QUARTERLY LEAD MEASUREMENTS AT NONURBAN STATIONS BY YEAR, 1970 THROUGH 1980 ($\mu g/m^3$)

Year	No. of station reports	Minimum qtrly. avg.	Percentile							Max. qtrly. avg.	Arithmetic		Geometric	
			10	30	50	70	90	95	99		Mean	Std. dev.	Mean	Std. dev.
1970	124	LD	LD	LD	LD	LD	0.267	0.383	0.628	1.471	--	--	--	--
1971	85	LD	LD	LD	LD	LD	0.127	0.204	0.783	1.134	--	--	--	--
1972	137	LD	LD	LD	0.107	0.166	0.294	0.392	0.950	1.048	0.139	0.169	0.90	2.59
1973	100	LD	LD	LD	LD	0.132	0.233	0.392	0.698	0.939	--	--	--	--
1974	79	LD	LD	0.053	0.087	0.141	0.221	0.317	0.496	0.534	0.111	0.111	0.083	2.30
1975	98	LD	LD	LD	LD	0.144	0.255	0.311	0.431	0.649	--	--	--	--
1976	98	LD	LD	LD	LD	0.105	0.240	0.285	0.336	0.483	--	--	--	--
1977	84	0.006	0.01	0.04	0.08	0.11	0.18	0.20	0.25	0.40	0.09	0.10	0.07	3.19
1978	20	0.002	0.007	0.04	0.06	0.09	0.24	0.33	0.33	0.33	0.08	0.10	0.07	2.84
1979	16	LD	0.02	0.02	0.10	0.14	0.21	0.27	0.32	0.11	0.11	0.13	0.11	3.45
1980	12	LD	0.01	0.005	0.03	0.05	0.11	0.13	0.13	0.13	0.04	0.06	0.05	3.33

Sources: Akland (1976); U.S. Environmental Protection Agency (1978; 1979); Quarterly averages of Lead from NFAN (1982).

TABLE 7A-3. NUMBER OF NASN NONURBAN STATIONS WHOSE DATA FALL WITHIN SELECTED ANNUAL AVERAGE LEAD CONCENTRATION INTERVALS, 1966-1980

Year		Concentration interval, $\mu g/m^3$				
		<0.03	0.03-0.096	0.10-0.19	0.20-0.45	Total
1966	No. stations	—	10	6	3	19
	Percent	—	52	32	16	100
1967	No. stations	1	7	10	2	20
	Percent	5	35	50	10	100
1968	No. stations	1	15	4	—	20
	Percent	5	75	20	—	100
1969	No. stations	—	11	9	1	21
	Percent	—	52	43	5	100
1970-1971	No. stations	—	—	7	3	10
	Percent	—	—	70	30	100
1972	No. stations	10	4	9	11	34
	Percent	29	12	26	33	100
1973	No. stations	9	7	6	1	23
	Percent	39	31	26	4	100
1974	No. stations	3	5	6	2	16
	Percent	19	31	38	12	100
1975	No. stations	0	0	1	4	5
	Percent	0	0	20	80	100
1976	No. stations	0	0	3	3	6
	Percent	0	0	50	50	100
1977	No. stations	5	8	7	1	21
	Percent	24	38	33	5	100
1978	No. stations	1	3	1	0	5
	Percent	20	60	20	0	100
1979	No. stations	1	1	1	1	4
	Percent	25	25	25	25	100
1980	No. stations	1	2	0	0	3
	Percent	33	67	0	0	100

Sources: Akland (1976); Shearer et al. (1972); U.S. Environmental Protection Agency (1978; 1979); Annual averages of lead from NFAN (1982).

APPENDIX 7B
SUPPLEMENTAL SOIL AND DUST INFORMATION

Lead in soil, and dust of soil origin, is discussed in Section 7.2.2. The data show average soil concentrations are 8 to 25 µg/g, and dust from this soil rarely exceeds 80 to 100 µg/g. Street dust, household dust and occupational dusts often exceed this level by one to two orders of magnitude. Tables 7B-1 and 7B-2 summarizes several studies of street dust. Table 7B-3 shows data on household and residential soil dust. These data support the estimates of mean lead concentrations in dust discussed in Section 7.3.1.4. Table 7B-4 gives airborne lead concentrations for an occupational setting, which are only qualitatively related to dust lead concentrations.

TABLE 7B-1. LEAD DUST ON AND NEAR HEAVILY TRAVELED ROADWAYS

Sampling site	Concentration, µg Pb/g	Reference
Washington, DC:		
Busy intersection	13,000	
Many sites	4000-8000	Fritsch and Prival (1972)
Chicago:		
Near expressway	6600	
Philadelphia:		
Near expressway	3000-8000	Kennedy (1973)
Brooklyn:		
Near expressway	900-4900	Lombardo (1973)
New York City:		
Near expressway	2000	Pinkerton et al. (1973)
Detroit:		
Street dust	970-1200	Ter Haar and Aronow (1974)
Philadelphia:		
Gutter (low pressure)	1500	
	210-2600	Shapiro et al. (1973)
Gutter (high pressure)	3300	
	280-8200	Shapiro et al. (1973)
Miscellaneous U.S. Cities:		
Highways and tunnels	10,000-20,000	Buckley et al. (1973)
Netherlands:		
Heavily traveled roads	5000	Rameau (1973)

TABLE 7B-2. LEAD CONCENTRATIONS IN STREET DUST IN LANCASTER, ENGLAND

Site	No. of samples	Range of concentrations	Mean	Standard deviation
Car parks	4	39,700 - 51,900	46,300	5,900
	16	950 - 15,000	4,560	3,700
Garage forecourts	2	44,100 - 48,900	46,500	--
	7	1,370 - 4,480	2,310	1,150
Town centre streets	13	840 - 4,530	2,130	960
Main roads	19	740 - 4,880	1,890	1,030
Residential areas	7	620 - 1,240	850	230
Rural roads	4	410 - 870	570	210

Source: Harrison (1979).

TABLE 7B-3. LEAD DUST IN RESIDENTIAL AREAS

Sampling site	Concentration, µg Pb/g	Reference
Philadelphia:		
Classroom	2000	
Playground	3000	
Window frames	1750	Shapiro et al. (1973)
Boston and New York:		
House dust	1000-2000	Needleman and Scanlon (1973)
Brattleboro, VT:		
In home	500-900	Darrow and Schroeder (1974)
New York City:		
Middle Class Residential	610-740	Pinkerton et al. (1973)
Philadelphia:		
Urban industrial	3900	
	930-16,000	Needleman et al. (1974)
Residential	610	
	290-1000	Needleman et al. (1974)
Suburban	830	
	280-1500	Needleman et al. (1974)
Derbyshire, England:		
Low soil lead area	520	
	130-3000	Barltrop et al. (1975)
High soil lead area	4900	
	1050-28,000	Barltrop et al. (1975)

TABLE 7B-4. AIRBORNE LEAD CONCENTRATIONS BASED ON PERSONAL SAMPLERS, WORN BY EMPLOYEES AT A LEAD MINING AND GRINDING OPERATION IN THE MISSOURI LEAD BELT

Air lead concentration (µg/m^3)

Occupation	N	High	Low	Mean
Mill operator	6	300	50	180
Flotation operator	4	750	100	320
Filter operator	4	2450	380	1330
Crusher operator	4	590	20	190
Sample finisher	2	10,000	7070	8530
Crusher utility	1	--	--	70
Shift boss	5	560	110	290
Equipment operator	1	--	--	430

N denotes number of air samples.
Source: Roy (1977).

APPENDIX 7C
STUDIES OF SPECIFIC POINT SOURCES OF LEAD

This collection of studies is intended to extend and detail the general picture of lead concentrations in proximity to identified major point sources as portrayed in Chapter 7. Because emissions and control technology vary between point sources, each point source is unique in the degree of environmental contamination. The list is by no means all-inclusive, but is intended to be representative and to supplement the data cited in Chapter 7. In many of the studies, blood samples of workers and their families were taken. These studies are also discussed in Chapter 11.

7C.1 SMELTERS AND MINES

7C.1.1 Two Smelter Study

The homes of workers of two unidentified secondary lead smelters in different geographical areas of the United States were studied by Rice et al. (1978). Paper towels were used to collect dust from surfaces in each house, following the method of Vostal et al. (1974). A total of 33 homes of smelter workers and 19 control homes located in the same or similar neighborhoods were investigated. The geometric mean lead levels on the towels were 79.3 µg (smelter workers) versus 28.8 µg (controls) in the first area, while in the second area mean values were 112 µg versus 9.7 µg. Also in the second area, settled dust above doorways was collected by brushing the dust into glassine envelopes for subsequent analysis. The geometric mean lead content of this dust in 15 workers' homes was 3300 µg/g, compared with 1200 µg/g in eight control homes. Curbside dust collected near each home in the second area had a geometric mean lead content of 1500 µg/g, with no significant difference between worker and control homes. No significant difference was reported in the paint lead content between worker and control homes. The authors concluded that lead in dust carried home by these workers contributed to the lead content of dust in their homes, despite showering and changing clothes at the plant, and despite work clothes being laundered by the company. Storage of employee street clothes in dusty lockers, walking across lead-contaminated areas on the way home, and particulate settling on workers' cars in the parking lot may have been important factors. Based on measurement of zinc protoporphyrin levels in the blood of children in these homes, the authors also concluded that the greater lead levels in housedust contributed to increased child absorption of lead.

7C.1.2 British Columbia, Canada

Neri et al. (1978) and Schmitt et al. (1979) examined environmental lead levels in the vicinity of a lead-zinc smelter at Trail, British Columbia. Total emissions from the smelter averaged about 135 kg Pb/day. Measurements were conducted in Trail (population 12,000), in Nelson, a control city 41 kilometers north of Trail (population 10,000), and in Vancouver. The annual mean airborne lead concentrations in Trail and in Nelson were 2.0 and 0.5 $\mu g/m^3$, respectively. Mean lead levels in surface soil were 1320 µg/g in Trail (153 samples), 192 µg/g in Nelson (55 samples), and 1545 µg/g in Vancouver (37 samples).

Blood lead measurements shows a positive correlation with soil lead levels for children aged 1-3 years and for first graders, but no significant correlation for ninth graders. The authors concluded that small children are most likely to ingest soil dust, and hence deposited smelter-emitted lead may pose a potential hazard for the youngest age group.

7C.1.3 Netherlands

Environmental lead concentrations were measured in 1978 near a secondary lead smelter in Arnhem, Netherlands (Diemel et al., 1981). Air and dust were sampled in over 100 houses at distances of 450 to 1000 meters from the smelter, with outdoor samples of air, dust, and soil collected for comparison. Results are presented in Table 7C-1. Note that the mean indoor concentration of total suspended particulates (TSP) is greater than the mean outdoor concentration, yet the mean indoor lead level is smaller than the corresponding outdoor level. The authors reasoned that indoor sources such as tobacco smoke, consumer products, and decay of furnishings are likely to be important in affecting indoor TSP; however, much of the indoor lead was probably carried in from the outside by the occupants, e.g., as dust adhering to shoes. The importance of resuspension of indoor particles by activity around the house was also discussed.

7C.1.4 Belgium

Roels et al. (1978; 1980) measured lead levels in the air, in dust, and on childrens' hands at varying distances from a lead smelter in Belgium (annual production 100,000 metric tons). Blood data from children living near the smelter were also obtained. Air samples were collected nearly continuously beginning in September 1973. Table 7C-2 lists the airborne concentrations recorded during five distinct population surveys between 1974 and 1978, while Figure 7C-1 presents air, dust, and hand data for Survey #3 in 1976. Statistical tests showed that blood lead levels were better correlated with lead on childrens' hands than with air lead. The authors suggested that ingestion of contaminated dust by hand-to-mouth activities

such as nail-biting and thumb-sucking, as well as eating with the hands, may be an important exposure pathway. It was concluded that intake from contaminated hands contributes at least two to four times as much lead as inhalation of airborne material.

TABLE 7C-1. LEAD CONCENTRATIONS IN INDOOR AND OUTDOOR AIR, INDOOR AND OUTDOOR DUST, AND OUTDOOR SOIL NEAR THE ARNHEM, NETHERLANDS SECONDARY LEAD SMELTER

(INDOOR CONCENTRATIONS)

Parameter	Arithmetic mean	Range	n*
Suspended particulate matter			
dust concentration ($\mu g/m^3$)	140	20-570	101
lead concentration ($\mu g/m^3$)	0.27	0.13-0.74	101
dust lead content ($\mu g/kg$)	2670	400-8200	106
Dustfall			
dust deposition ($mg/m^3 \cdot day$)	15.0	1.4-63.9	105
lead deposition ($\mu g/m^3 \cdot day$)	9.30	1.36-42.4	105
dust lead content (mg/kg)	1140	457-8100	105
Floor dust			
amount of dust (mg/m^3)	356	41-2320	107
amount of lead ($\mu g/m^3$)	166	18-886	101
Dust lead content (mg/kg)			
in "fine" floor dust	1050	463-4740	107
in "coarse" floor dust	370	117-5250	101

*N number of houses.

(OUTDOOR CONCENTRATIONS)

Parameter	Arithmetic mean	Range
Suspended particles		
dust concentration ($\mu g/m^3$)	64.5	53.7-73.3
lead concentraton ($\mu g/m^3$) (high-volume samplers, 24-hr samples, 2 months' average)	0.42	0.28-0.52
Lead in dustfall ($\mu g/m^3 \cdot day$) (deposit gauges, weekly samples, 2 months' average)	508	208-2210
Lead in soil (mg/kg 0-5 cm)	322	21-1130
Lead in streetdust (mg/kg <0.3 mm)	860	77-2670

Source: Diemel et al (1981).

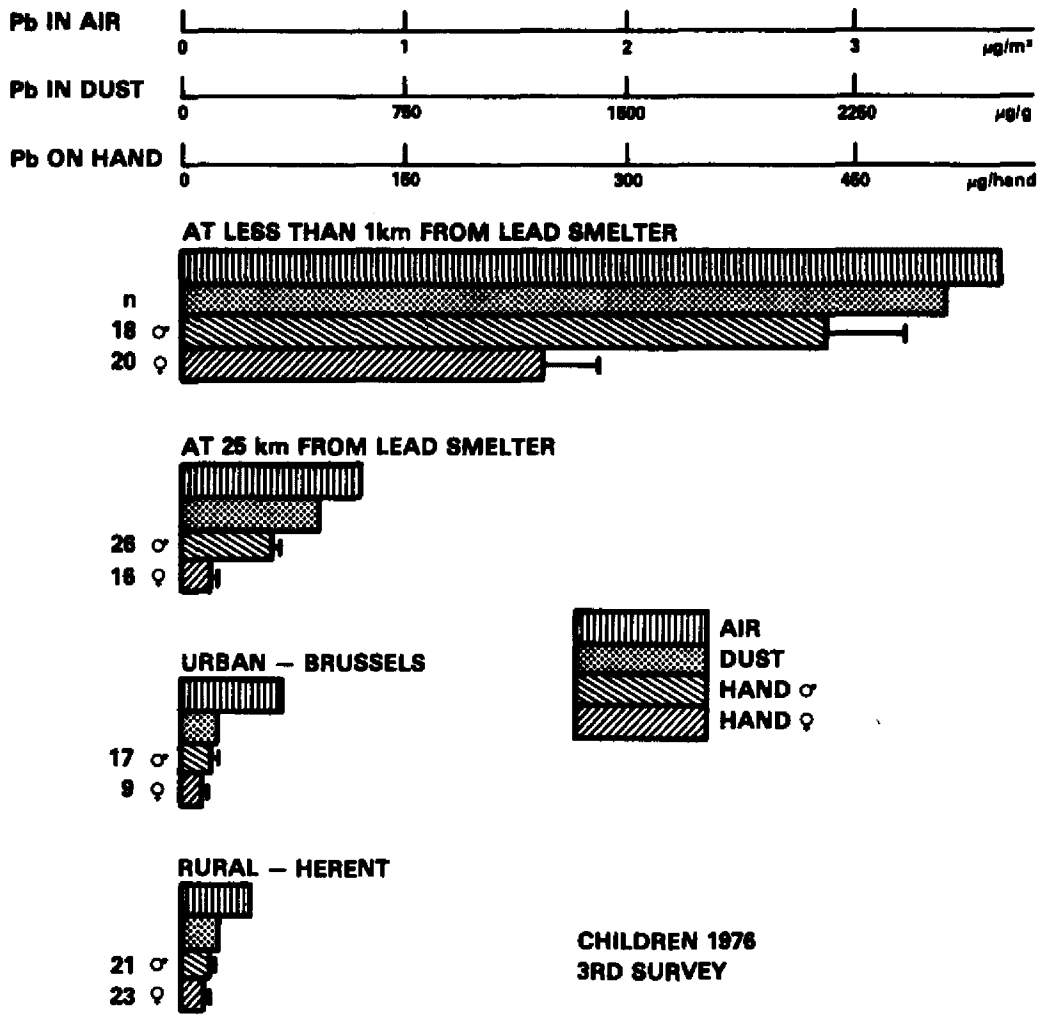

Figure 7C-1. Concentrations of lead in air, in dust, and on children's hands, measured during the third population survey of Table E. Values obtained less than 1 km from the smelter, at 2.5 km from the smelter, and in two control areas are shown.
Source: Roels et al. (1980).

TABLE 7C-2. AIRBORNE CONCENTRATIONS OF LEAD DURING FIVE POPULATION SURVEYS NEAR A LEAD SMELTER IN BELGIUM*

Study populations		Pb-Air ($\mu g/m^3$)
1 Survey (1974)	<1 km	4.06
	2.5 km	1.00
	Rural	0.29
2 Survey (1975)	<1 km	2.94
	2.5 km	0.74
	Rural	
3 Survey (1976)	<1 km	3.67
	2.5 km	0.80
	Urban	0.45
	Rural	0.30
4 Survey (1977)	<1 km	3.42
	2.5 km	0.49
5 Survey (1978)	<1 km	2.68
	2.5 km	0.54
	Urban	0.56
	Rural	0.37

*Additional airborne data in rural and urban areas obtained as controls are also shown.

Source: Roels et al. (1980).

7C.1.5 Meza River Valley, Yugoslavia

In 1967, work was initiated in the community of Zerjav, situated in the Slovenian Alps on the Meza River, to investigate contamination by lead of the air, water, snow, soil, vegetation, and animal life, as well as the human population. The mselter in this community produces about 20,000 metric tons of lead annually; until 1969 the stack emitted lead oxides without control by filters or other devices. Five sampling sites with high-volume samplers operating on a 24-hr basis were established in the four principal settlements within the Meza River Valley (Figure 7C-2): (1) Zerjav, in the center, the site of the smelter, housing 1503 inhabitants, (2) Rudarjevo, about 2 km to the south of Zerjav with a population of 100; (3) Crna, some 5 km to the southwest, population 2198, where there are two sites (Crna-SE and Crna-W); and (4) Mezica, a village about 10 km to the northwest of the smelter with 2515

inhabitants. The data in Table 7C-3 are sufficient to depict general environmental contamination of striking proportions.

7C.1.6 Kosova Province, Yugoslavia

Popovac et al. (1982) discuss lead exposure in an industrialized region near the town of Kosova Mitrovica, Yugoslavia, containing a lead smelter and refinery, and a battery factory. In 1979, 5800 kg of lead were emitted daily from the lead smelter alone. Ambient air concentrations in the town were in the range 21.2 to 29.2 $\mu g/m^3$ in 1980, with levels occasionally reaching 70 $\mu g/m^3$. The authors report elevated blood lead levels in most of the children tested; some extremely high values were found, suggesting the presence of congenital lead poisoning.

7C.1.7 Czechoslovakia

Wagner et al. (1981) measured total suspended particulate and airborne lead concentrations in the vicinity of a waste lead processing plant in Czechoslovakia. Data are shown in Table 7C-4. Blood lead levels in 90 children living near the plant were significantly greater than in 61 control children.

7C.1.8 Australia

Heyworth et al. (1981) examined child response to lead in the vicinity of a lead sulfide mine in Northhamptom Western Australia. Two samples of mine tailings measured in 1969 contained 12,000 µg/g and 28,000 µg/g lead; several additional samples analyzed in 1978 contained 22,000 µg/g to 157,000 µg/g lead. Surface soil from the town boundry contained 300 µg/g, while a playground and a recreational area had soil containing 11,000 µg/g and 12,000 µg/g lead respectfully.

Blood lead levels measured in Northhamptom children, near the mine, were slightly greater than levels measured in children living a short distance away. The Northhampton blood lead levels were also slightly greater than those reported for children in Victoria, Australia (DeSilva and Donnan, 1980). Heyworth et al. concluded that the mine tailings could have increased the lead exposure of children living in the area.

7C.2 BATTERY FACTORIES

7C.2.1 Southern Vermont

Watson et al. (1978) investigated homes of employees of a lead storage battery plant in southern Vermont in August and September, 1976. Lead levels in household dust, drinking water, and paint were determined for 22 workers' homes and 22 control homes. The mean lead

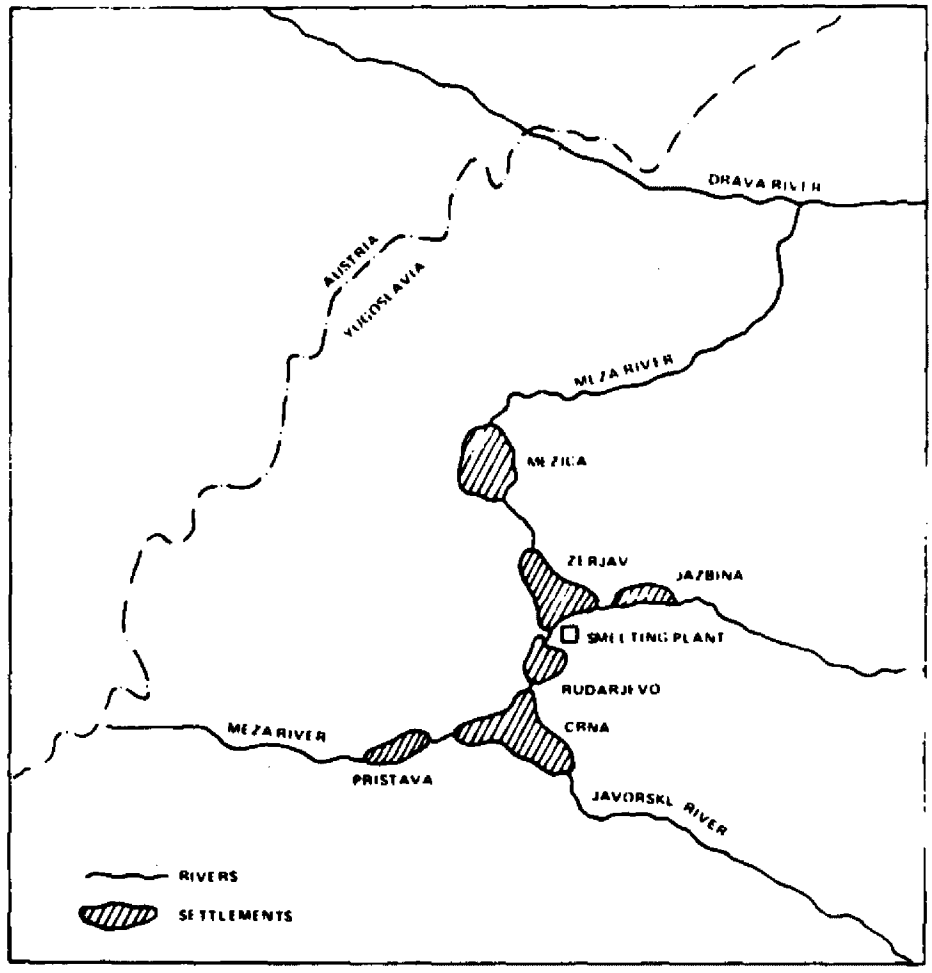

Figure 7C-2. Schematic plan of lead mine and smelter from Meza Valley, Yugoslavia, study.

Source: Fugas (1977).

Table 7C-3. ATMOSPHERIC LEAD CONCENTRATIONS (24-hour) IN THE MEZA VALLEY, YUGOSLAVIA, NOVEMBER 1971 TO AUGUST 1972

Site	Pb concentration, $\mu g/m^3$		
	Minimum	Maximum	Average
Mezica	0.1	236.0	24.2
Zerjav	0.3	216.5	29.5
Rudarjevo	0.5	328.0	38.4
Crna SE	0.1	258.5	33.7
Crna W	0.1	222.0	28.4

Source: Fugas (1977).

TABLE 7C-4. CONCENTRATIONS OF TOTAL AIRBORNE DUST AND OF AIRBORNE LEAD IN THE VICINITY OF A WASTE LEAD PROCESSING PLANT IN CZECHOSLOVAKIA, AND IN A CONTROL AREA INFLUENCED PREDOMINANTLY BY AUTOMOBILE EMISSIONS

		TSP	Lead
Exposed	n	300	303
	$\bar{x}$ ($\mu g/m^3$)	113.6	1.33
	S	83.99	1.9
	range	19.7-553.4	0.12-10.9
	95% c.i.	123.1-104.1	1.54-1.11
Control	n	56.0	87
	$\bar{x}$ ($\mu g/m^3$)	92.0	0.16
	S	40.5	0.07
	range	10-210	0.03-0.36
	95% c.i.	102.7-81.3	0.17-0.14

n = number of samples; $\bar{x}$ = mean of 24-hour samples;
s = standard deviation; 95% confidence interval.

Source: Wagner et al. (1981).

concentration in dust in the workers' homes was 2,200 µg/g, compared with 720 µg/g in the control homes. Blood lead levels in the workers' children were greater than levels in the control children, and were significantly correlated with dust lead concentrations. No significant correlations were found between drinking water lead and blood lead, or between paint lead and blood lead. It is noteworthy that although 90 percent of the employees showered and changed clothes at the plant, 87 percent brought their work clothes home for laundering. The authors concluded that dust carried home by the workers contributed to increased lead absorption in their children.

7C.2.2 North Carolina

Several cases of elevated environmental lead levels near point sources in North Carolina have been reported by Dolcourt et al. (1978; 1981). In the first instance, dust lead was measured in the homes of mothers employed in a battery factory in Raleigh; blood lead levels in the mothers and their children were also measured. Carpet dust was found to contain 1,700 to 48,000 µg/g lead in six homes where the children had elevated blood lead levels (>40 µg/dl). The authors concluded that lead carried home on the mothers' clothing resulted in increased exposure to their children (Dolcourt et al., 1978). In this particular plant, no uniforms or garment covers were provided by the factory; work clothing was worn home.

In a second case, discarded automobile battery casings from a small-scale lead recovery operation in rural North Carolina were brought home by a worker and used in the family's wood-burning stove (Dolcourt et al., 1981). Two samples of indoor dust yielded 13,000 and 41,000 µg/g lead. A three-year-old girl living in the house developed encephalopathy resulting in permanent brain damage.

In a third case, also in rural North Carolina, a worker employed in an automobile battery reclamation plant was found to be operating an illicit battery recycling operation in his home. Reclaimed lead was melted on the kitchen stove. Soil samples obtained near the house measured as high as 49 percent lead by weight; the driveway was covered with fragments of battery casings. Although no family member had evidence of lead poisoning, there were unexplained deaths among chickens who fed where the lead waste products were discarded (Dolcourt et al., 1981).

7C.2.3 Oklahoma

Morton et al. (1982) studied lead exposure in children of employees at a battery manufacturing plant in Oklahoma. A total of 34 lead-exposed children and 34 control children were examined during February and March, 1978; 18 children in the lead-exposed group had elevated blood lead levels (>30 µg/dl), while none of the controls were in this category.

It was found that many of the battery factory employees also used lead at home, such as casting lead into fishing sinkers and using leaded ammunition. A significant difference in blood lead levels between the two groups of children was found even when families using lead at home were deleted from the data set. Using the results of personal interviews with the homemaker in each household, the authors concluded that dust carried home by the employees resulted in increased exposure of their children. Merely changing clothes at the plant was deemed insufficient to avoid transporting appreciable amounts of lead home: showering and shampooing, in addition to changing clothes, was necessary.

7C.2.4 Oakland, California

Environmental lead contamination at the former site of wet-cell battery manufacturing plant in Oakland, California was reported by Wesolowski et al. (1979). The plant was operational from 1924 to 1974, and was demolished in 1976. Soil lead levels at the site measured shortly after demolition are shown in Table 7C-5. The increase in median concentrations with depth suggested that the battery plant, rather than emissions from automobiles, were responsible for the elevated soil lead levels. The levels decreased rapidly below 30 cm depth. The contaminated soil was removed to a sanitary landfill and replaced with clean soil; a park has subsequently been constructed at the site.

TABLE 7C-5. LEAD CONCENTRATIONS IN SOIL AT THE FORMER SITE OF A WET-CELL BATTERY MANUFACTURING PLANT IN OAKLAND, CALIFORNIA

Depth	N	Range (μg/g)	Mean (μg/g)	Median (μg/g)
Surface	24	57-96,000	4300	200
15 cm	23	13-4200	370	200
30 cm	24	13-4500	1100	360

Source: Wesolowski et al. (1979).

7C.2.5 Manchester, England

Elwood et al. (1977) measured lead concentrations in air, dust, soil, vegetation, and tap water, as well as in the blood of children and adults, in the vicinity of a large battery factory near Manchester. It was found that lead levels in dust, soil, and vegetation decreased with increasing distance from the factor. Airborne lead concentrations did not show a consistent effect with downwind distance, although higher concentrations were found downwind

compared with upwind of the factor. Blood lead levels were greatest in the households of battery factor employees: other factors such as distance from the factory, car ownership, age of house, and presence of lead water pipes were outweighed by the presence of a leadworker in the household. These results strongly suggest that lead dust carried home by the factor employees is a dominant exposure pathway for their families. The authors also discussed the work of Burrows (1976), who demonstrated experimentally that the most important means of lead transport from the factory into the home is via the workers' shoes.

APPENDIX 7D

SUPPLEMENTAL DIETARY INFORMATION FROM THE U.S. FDA TOTAL DIET STUDY

The U.S. Food and Drug Administration published a new Total Diet Food List (Pennington, 1983) based on over 100,000 daily diets from 50,000 participants. Thirty five hundred categories of foods were condensed to 201 adult food categories for 8 age/sex groups. Summaries of these data were used in Section 7.3.1.2 to arrive at lead exposures through food, water, and beverages. For brevity and continuity with the crop data of Section 7.2.2.2.1, it was necessary to condense the 201 categories of the Pennington study to 25 categories in this report.

The preliminary lead concentrations for all 201 items of the food list were provided by U.S. Food and Drug Administration (1983). These data represent three of the four Market Basket Surveys, the fourth to be provided at a later time. Means of these values have been calculated by EPA, using one-half the detection limit for values reported below detection limit. These data appear in Table 7D-1.

In condensing the 201 categories of Table 7D-1 to the 25 categories of Table 7-15, combinations and fractional combinations of categories were made according to the scheme of Table 7D-2. In this way, specific categories of food more closely identified with farm products were summarized. The assumptions made concerning the ingredients in the final product, (mainly water, flour, eggs, and milk) had little influence on the outcome of the summarization.

TABLE 7D-1. FOOD LIST AND PRELIMINARY LEAD CONCENTRATIONS

Category	Food	Lead concentration* (µg/g)			Mean+
1	Whole milk				0.01
2	Low fat milk	0.02	T	T	0.017
3	Chocolate milk			0.04	0.02
4	Skim milk				0.01
5	Butter milk				0.01
6	Yogurt, plain				0.01
7	Milkshake	0.06	0.05		0.04
8	Evaporated milk	0.08	0.07	0.18	0.11
9	Yogurt, sweetened	0.04			0.02
10	Cheese, American	0.03			0.97
11	Cottage cheese	0.05			0.023
12	Cheese, Cheddar	0.04			0.020
13	Beef, ground		0.11		0.043
14	Beef, chuck roast	0.09		0.03	0.043
15	Beef, round steak				0.01
16	Beef, sirloin				0.01
17	Pork, ham		0.03		0.017
18	Pork chop		0.03		0.017
19	Pork sausage	0.03	0.05		0.030
20	Pork, bacon	0.05	0.22		0.093
21	Pork roast				0.01
22	Lamb chop		0.03		0.017
23	Veal cutlet				0.01
24	Chicken, fried	0.04			0.020
25	Chicken, roasted				0.01
26	Turkey, roasted				0.01
27	Beef liver	0.11	0.12		0.08
28	Frankfurters				0.01
29	Bologna	0.02			0.013
30	Salami				0.01
31	Cod/haddock filet		0.07		0.03
32	Tuna, canned	0.18	0.27	0.08	0.18
33	Shrimp			0.10	0.04
34	Fish sticks, frozen		0.03		0.017
35	Eggs, scrambled				0.01
36	Eggs, fried	0.03			0.017
37	Eggs, soft boiled				0.01
38	Pinto beans, dried	0.04	0.02		0.023
39	Pork and beans, canned	0.41	0.07	0.04	0.17
40	Cowpeas, dried				0.01
41	Lima beans, dried		0.03		0.017
42	Lima beans, frozen		0.03		0.017
43	Navy beans, dried	0.03			0.017
44	Red beans, dried	0.02	0.06		0.03

TABLE 7D-1. (continued)

Category	Food	Lead concentration* (µg/g)			Mean+
45	Peas, green, canned	0.14	0.28	0.25	0.22
46	Peas, green, frozen	0.03	0.08		0.04
47	Peanut butter	0.15			0.56
48	Peanuts				0.01
49	Pecans	0.03			0.017
50	Rice, white	0.05	0.19		0.084
51	Oatmeal	0.06			0.027
52	Farina	0.03			0.017
53	Corn grits				0.01
54	Corn, frozen	T	T		0.013
55	Corn, canned	0.22	0.56	0.06	0.28
56	Corn, cream style, canned	0.09	0.06	0.11	0.09
57	Popcorn		0.07	0.08	0.053
58	White bread				0.01
59	Rolls, white	0.03	0.06	0.02	0.037
60	Cornbread				0.01
61	Biscuits	0.04		0.02	0.023
62	Whole wheat bread	0.05		0.03	0.03
63	Tortilla	0.02	0.03	0.02	0.023
64	Rye bread	0.03		0.02	0.02
65	Muffins				0.01
66	Crackers, saltine			0.03	0.017
67	Corn chips		0.04		0.02
68	Pancakes		0.03		0.017
69	Noodles	0.04	0.05		0.033
70	Macaroni		0.02		0.013
71	Corn flakes		0.04		0.02
72	Pre-sweetened cereal		0.06	0.03	0.033
73	Shredded wheat cereal				0.01
74	Raisin bran cereal			0.03	0.017
75	Crisped rice cereal			0.02	0.013
76	Granola	0.03		0.02	0.02
77	Oat ring cereal	0.03	0.02	0.04	0.03
78	Apple, raw	0.04	0.04		0.03
79	Orange, raw		0.03	0.02	0.02
80	Banana, raw				0.01
81	Watermelon, raw			0.02	0.013
82	Peach, canned	0.18	0.23	0.28	0.23
83	Peach, raw	0.02	0.04		0.023
84	Applesauce, canned	0.21	0.19	0.10	0.17
85	Pear, raw	0.02	0.03		0.02
86	Strawberries, raw	0.03			0.017
87	Fruit cocktail, canned	0.23	0.24	0.13	0.20
88	Grapes, raw		0.02		0.013
89	Cantaloupe, raw	0.03	0.08		0.04
90	Pear, canned	0.24	0.22	0.17	0.31
91	Plums, raw	T			0.012
92	Grapefruit, raw	0.03			0.017
93	Pineapple, canned	0.10	0.08	0.05	0.08

TABLE 7D-1. (continued)

Category	Food	Lead concentration* (µg/g)			Mean+
94	Cherries, raw		0.03		0.017
95	Raisins, dried	0.04		0.04	0.03
96	Prunes, dried	0.05		0.04	0.033
97	Avocado, raw	0.03	0.07		0.037
98	Orange juice, frozen	0.02			0.013
99	Apple juice, canned	0.06	0.09	0.02	0.054
100	Grapefruit juice, frozen	0.03	0.04		0.027
101	Grape juice, canned	0.06	0.11	0.04	0.07
102	Pineapple juice, canned	0.08	0.02	0.05	0.05
103	Prune juice, bottled	0.02		0.02	0.017
104	Orange juice, canned	0.05	0.03	0.02	0.033
105	Lemonade, frozen	0.04	0.07		0.03
106	Spinach, canned	0.80	1.65	0.12	0.86
107	Spinach, frozen	0.05	0.10	0.06	0.07
108	Collards, frozen	0.05	0.27	0.04	0.12
109	Lettuce, raw				0.01
110	Cabbage, raw	0.03			0.017
111	Coleslaw	0.13			0.05
112	Sauerkraut, canned	0.77	0.39	0.12	0.43
113	Broccoli, frozen	0.04	0.03		0.027
114	Celery, raw				0.01
115	Asparagus, frozen	0.02			0.013
116	Cauliflower, frozen				0.01
117	Tomato, raw	0.03			0.017
118	Tomato juice, canned	0.16	0.04	T	0.072
119	Tomato sauce, canned	0.26	0.31	0.12	0.23
120	Tomatoes, canned	0.19	-	0.23	0.21
121	Beans, snap green, frozen	0.03		0.02	0.02
122	Beans, snap green, canned	0.14	0.23	0.12	0.16
123	Cucumber, raw		T		0.012
124	Squash, summer, frozen	0.04	0.02		0.023
125	Pepper, green, raw	0.07	0.02		0.033
126	Squash, winter, frozen	0.02			0.013
127	Carrots, raw		0.03		0.017
128	Onion, raw		0.05	0.02	0.027
129	Vegetables, mixed, canned		0.17	0.06	0.08
130	Mushrooms, canned	0.25	0.25	0.12	0.21
131	Beets, canned	0.17	0.11	0.08	0.12
132	Radish, raw	0.03	0.03		0.023
133	Onion rings, frozen	0.07	0.02		0.033
134	French fries, frozen		T		0.012
135	Mashed potatoes, instant	0.11			0.043
136	Boiled potatoes, w/o peel		0.02		0.013
137	Baked potato, w/ peel		0.04	0.02	0.023
138	Potato chips	0.03			0.017
139	Scalloped potatoes	0.04	0.02		0.023
140	Sweet potato, baked		0.05	0.04	0.033
141	Sweet potato, candied	0.04	0.04	0.02	0.033
142	Spaghetti, w/ meat sauce	0.11	0.12	0.08	0.10
143	Beef and vegetable stew		T		0.012

TABLE 7D-1. (continued)

Category	Food	Lead concentration* (µg/g)			Means+
144	Pizza, frozen	0.06	0.03		0.033
145	Chili, beef and beans	0.12	0.05		0.06
146	Macaroni and cheese				0.01
147	Hamburger sandwich	0.02			0.013
148	Meatloaf	0.06	0.46		0.17
149	Spaghetti in tomato sauce, canned	0.06	0.02		0.03
150	Chicken noodle casserole		0.04		0.02
151	Lasagne	0.11	0.06	0.03	0.067
152	Potpie, frozen	0.04	0.03		0.027
153	Pork chow mein	0.32	0.03	0.04	0.13
154	Frozen dinner				0.01
155	Chicken noodle soup, canned	0.02	0.02	0.06	0.033
156	Tomato soup, canned	0.07	0.02	T	0.035
157	Vegetable beef soup, canned	0.04	0.04	0.04	0.04
158	Beef bouillon, canned		0.02		0.013
159	Gravy mix	0.02			0.013
160	White sauce	0.05	0.02		0.027
161	Pickles	0.10	0.09		0.67
162	Margarine	0.06	0.06		0.043
163	Salad dressing	0.03	0.06		0.033
164	Butter		0.14		0.053
165	Vegetable oil				0.01
166	Mayonnaise				0.01
167	Cream	0.06			0.027
168	Cream substitute	0.10	0.04		0.05
169	Sugar	0.07	0.05		0.043
170	Syrup	0.06			0.027
171	Jelly		0.05		0.023
172	Honey	0.12	0.06		0.063
173	Catsup			0.02	0.013
174	Ice cream	0.03	0.02	0.03	0.027
175	Pudding, instant				0.01
176	Ice cream sandwich	0.05	0.02		0.027
177	Ice milk	0.07	0.04	0.02	0.043
178	Chocolate cake	0.13	0.03		0.057
179	Yellow cake	0.16			0.06
180	Coffee cake	0.04	0.03	0.05	0.04
181	Doughnuts	0.02			0.013
182	Danish pastry	0.06			0.037
183	Cookies, choc. chip	0.04	0.03	0.03	0.033
184	Cookies, sandwich type	0.03	0.03	0.04	0.027
185	Apple pie, frozen	0.04		0.02	0.023
186	Pumpkin pie	0.05	0.02	0.03	0.033
187	Candy, milk chocolate	0.09	0.04	0.09	0.07
188	Candy, caramels		0.04	0.04	0.03
189	Chocolate powder	0.06	0.03	0.08	0.06
190	Gelatin dessert	0.02		T	0.015
191	Soda pop, cola, canned		0.02		0.013

TABLE 7D-1. (continued)

Category	Food	Lead concentration* (μg/g)			Mean+
192	Soda pop lemon-lime, canned	0.13	0.02	0.02	0.06
193	Soft drink powder		0.02		0.013
194	Soda pop, cola, low cal., canned	0.05	0.02		0.027
195	Coffee, instant				0.01
196	Coffee, instant, decaf.		0.02		0.013
197	Tea				0.01
198	Beer, canned	0.02	0.02		0.17
199	Wine	0.03	0.03	0.03	0.03
200	Whiskey	0.02			0.013
201	Water	T			0.012

*Individual values for three Market Basket Surveys. "T" means only a trace detected, missing value means below detection limit.
+Means determined by EPA using 0.01 (½ of detection limit) for missing values and 0.015 for "T".

TABLE 7D-2. CONDENSATION, TO 25 CATEGORIES, OF THE 201 CATEGORIES OF FOOD

Table 7-13 category	Categories and fractional categories* from Pennington (1983) (Table 7D-1)
Milk	1-6, 9
Dairy Products	7, 10-12, 164, 167, 174, 176, 177
Milk as ingredient	0.5(156), 0.2(178-187)
Beef	13-16, 0.1(143), 0.3(145), 0.6(147, 0.4(142, 149)
Pork	17-21
Chicken	24-26
Fish	31-34
Prepared meats	28-30
Other meats	22-23, 27
Eggs	35-37, 0.15(142, 144, 146, 149), 0.2(178-187), 0.3(69, 70)
Bread	58, 59, 61, 62, 65, 66, 0.4(147)
Flour as ingredient	159, 160, 0.3(142, 144, 146, 149, 178-187), 0.6(69, 70)
Non-wheat cereals	50-52, 64, 75-77
Corn flour	53, 60, 63, 67, 71
Leafy vegetables	107-111, 113-116
Root vegetables	127, 128, 132
Vine vegetables	38, 40-44, 46, 117, 121, 123-126, 161, 173
Canned vegetables	39, 45, 106, 112, 118-120, 122, 129-131, 0.1(142, 145, 149) 0.2(144), 0.5(155-157)
Sweet corn	54
Canned sweet corn	55, 56
Potatoes	134-141
Vegetable oil	162, 163, 165, 166
Sugar	169-172, 188, 0.3(178-187)
Canned fruits	82, 84, 87, 90, 93
Fresh fruits	78-81, 83, 85, 86, 88, 89, 91, 92, 94-97

*In some cases, only a fraction of a category, e.g., milk in tomato soup, was used, and this fraction is indicated by a decimal fraction before the category number in parenthesis.

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8. EFFECTS OF LEAD ON ECOSYSTEMS

8.1 INTRODUCTION

8.1.1 Scope of Chapter 8

This chapter describes the potential effects of atmospheric lead inputs on several types of ecosystems. An effect is any condition attributable to lead that causes an abnormal physiological response in individual organisms or that perturbs the normal processes of an ecosystem. A distinction is made among natural, cultivated, and urban ecosystems, and extended discussions are included on the mobility and bioavailability of lead in ecosystems.

There are many reports on the effects of lead on individual populations of plants and animals and a few studies on the effects of lead in simulated ecosystems or microcosms. However, the most realistic studies are those that examine the effects of lead on entire ecosystems, as they incorporate all of the ecological interactions among the various populations and all of the chemical and biochemical processes relating to lead (National Academy of Sciences, 1981). Unfortunately, these studies have also had to cope with the inherent variability of natural systems and the confounding frustrations of large scale projects. Consequently, there are only a handful of ecosystem studies on which to base this report.

The principle sources of lead entering an ecosystem are: the atmosphere (from automotive emissions), paint chips, spent ammunition, the application of fertilizers and pesticides, and the careless disposal of lead-acid batteries or other industrial products. Atmospheric lead is deposited on the surfaces of vegetation as well as on ground and water surfaces. In terrestrial ecosystems, this lead is transferred to the upper layers of the soil surface, where it may be retained for a period of several years. The movement of lead within ecosystems is influenced by the chemical and physical properties of lead and by the biogeochemical properties of the ecosystem. Lead is non-degradable, but in the appropriate chemical environment, may undergo transformations which affect its solubility (e.g., formation of lead sulfate in soils), its bioavailability (e.g., chelation with humic substances), or its toxicity (e.g., chemical methylation).

The previous Air Quality Criteria for Lead (U.S. Environmental Protection Agency, 1977) recognized the problems of atmospheric lead exposure incurred by all organisms including man. Emphasis in the chapter on ecosystem effects was given to reports of toxic effects on specific groups of organisms, e.g. domestic animals, wildlife, aquatic organisms, and vascular and nonvascular plants. Forage containing lead at 80 μg/g dry weight was reported to be lethal to horses, whereas 300 μg/g dry weight caused lethal clinical symptoms in cattle. This report will attempt to place the data in the context of sublethal effects of lead exposure, to extend the conclusions to a greater variety of domestic animals, and to describe the types and ranges of exposures in ecosystems likely to present a problem for domestic animals.

Research on lead in wildlife has traditionally fallen into the following somewhat artificial categories: waterfowl; birds and small mammals; fish; and invertebrates. In all these categories, no correlation could be made in the 1977 report between toxic effects and environmental concentrations. Some recent toxicity studies have been completed on fish and invertebrates and the data are reported below, but there is still little information on the levels of lead that can cause toxic effects in small mammals or birds.

Information on the relationship between soil lead and plants can be expanded somewhat beyond the 1977 report, primarily due to a better understanding of the role of humic substances in binding lead. Although the situation is extremely complex, it is reasonable to state that most plants cannot survive in soil containing 10,000 µg/g dry weight if the pH is below 4.5 and the organic content is below 5 percent. The specifics of this statement are discussed more extensively in Section 8.3.1.2.

Before 1977, natural levels of lead in environmental media other than soil were not well known. Reports of sublethal effects of lead were sparse and there were few studies of total ecosystem effects. Although several ecosystem studies have been completed since 1977 and many problems have been overcome, it is still difficult to translate observed effects under specific conditions directly to predicted effects in ecosystems. Some of the known effects, which are documented in detail in the appropriate sections, are summarized here:

Plants. The basic effect of lead on plants is to stunt growth. This may be through a reduction of photosynthetic rate, inhibition of respiration, cell elongation, or root development, or premature senescence. Some genetic effects have been reported. All of these effects have been observed in isolated cells or in hydroponically-grown plants in solutions comparable to 1 to 2 µg/g soil moisture. These concentrations are well above those normally found in any ecosystem except near smelters or roadsides. Terrestrial plants take up lead from the soil moisture and most of this lead is retained by the roots. There is no evidence for foliar uptake of lead and little evidence that lead can be translocated freely to the upper portions of the plant. Soil applications of calcium and phosphorus may reduce the uptake of lead by roots.

Animals. Lead affects the central nervous system of animals and their ability to synthesize red blood cells. Blood concentrations above 0.4 ppm (40 µg/dl) can cause observable clinical symptoms in domestic animals. Calcium and phosphorus can reduce the intestinal absorption of lead. The physiological effects of lead exposures in laboratory animals are discussed in extensive detail in Chapters 10 and 12 of this document.

Microorganisms. There is evidence that lead at environmental concentrations occasionally found near roadsides and smelters (10,000 to 40,000 µg/g dw) can eliminate populations of bacteria and fungi on leaf surfaces and in soil. Many of those micoorganisms play key roles in the decomposition food chain. It is likely that the affected microbial populations are replaced by others of the same or different species, perhaps less efficient at decomposing organic matter. There is also evidence that microorganisms can mobilize lead by making it more soluble and more readily taken up by plants. This process occurs when bacteria exude organic acids that lower the pH in the immediate vicinity of the plant root.

Ecosystems. There are three known conditions under which lead may perturb ecosystem processes. At soil concentrations of 1,000 µg/g or higher, delayed decomposition may result from the elimination of a single population of decomposer microorganisms. Secondly, at concentrations of 500 to 1,000 µg/g, populations of plants, microorganisms, and invertebrates may shift toward lead tolerant populations of the same or different species. Finally, the normal biogeochemical process which purifies and repurifies calcium in grazing and decomposer food chains may be circumvented by the addition of lead to vegetation and animal surfaces. This third effect can be measured at all ambient atmospheric concentrations of lead.

Some additional effects may occur due to the uneven distribution of lead in ecosystems. It is known that lead

accumulates in soil, especially soil with high organic content. Although no firm documentation exists, it is reasonable to assume from the known chemistry of lead in soil that: 1) other metals may be displaced from the binding sites on the organic matter; 2) the chemical breakdown of inorganic soil fragments may be retarded by the interference of lead on the action of fulvic acid on iron bearing crystals; and 3) lead in soil may be in equilibrium with moisture films surrounding soil particles and thus available for uptake by plants.

To aid the reader in understanding the effects of lead on ecosystems, sections have been included that discuss such important matters as how ecosystems are organized, what processes regulate metal cycles, what criteria are valid in interpreting ecosystem effects, and how soil systems function to regulate the controlled release of nutrients to plants. The informed reader may wish to turn directly to Section 8.3, where the discussion of the effects of lead on organisms begins.

8.1.2 Ecosystem Functions

8.1.2.1 Types of Ecosystems. Based on ambient concentrations of atmospheric lead and the distribution of lead in the soil profile, it is useful to distinguish among three types of ecosystems: natural, cultivated, and urban. Natural ecosystems include aquatic and terrestrial ecosystems that are otherwise unperturbed by man, and those managed ecosystems, such as commercial forests, grazing areas, and abandoned fields, where the soil profile has remained undisturbed for several decades. Cultivated ecosystems include those where the soil profile is frequently disturbed and those where chemical fertilizers, weed killers, and pest-control agents may be added. In urban ecosystems, a significant part of the exposed surface includes rooftops, roadways, and parking lots from which runoff, if not channeled into municipal waste processing plants, is spread over relatively small areas of soil surface. The ambient air concentration of lead in urban ecosystems is 5 to 10 times higher than in natural or cultivated ecosystems (See Chapter 7). Urban ecosystems may also be exposed to lead from other than atmospheric sources, such as paint, discarded batteries, and used motor oil. The effects of atmospheric lead depend on the type of ecosystems examined.

8.1.2.2 Energy Flow and Biogeochemical Cycles. Two principles govern ecosystem functions: 1) energy flows through an ecosystem; and 2) nutrients cycle within an ecosystem. Energy

usually enters the ecosystem in the form of sunlight and leaves as heat of respiration. Stored chemical energy may be transported into or out of an ecosystem (e.g., leaf detritus in a stream) or be retained by the ecosystem for long periods of time (e.g., tree trunks). Energy flow through an ecosystem may give structure to the ecosystem by establishing food webs which efficiently regulate the transfer of energy. Segments of these food webs are called food chains. Energy that flows along a grazing food chain is diverted at each step to the detrital food chain.

Unlike energy, nutrient and non-nutrient elements are recycled by the ecosystem and transferred from reservoir to reservoir in a pattern usually referred to as a biogeochemical cycle (Brewer, 1979, p. 139). The reservoirs correspond approximately to the food webs of energy flow. Although elements may enter (e.g., weathering of soil) or leave the ecosystem (e.g., stream runoff), the greater fraction of the available mass of the element is usually cycled within the ecosystem.

Two important characteristics of a reservoir are the amount of the element that may be stored in the reservoir and the rate at which the element enters or leaves the reservoir. Some reservoirs may contain a disproportionately large amount of a given element. For example, most of the carbon in a forest is bound in the trunks and roots of trees, whereas most of the calcium may be found in the soil (Smith, 1980, p. 316). Some large storage reservoirs, such as soil, are not actively involved in the rapid exchange of the nutrient element, but serve as a reserve source of the element through the slow exchange with a more active reservoir, such as soil moisture. When inputs exceed outputs, the size of the reservoir increases. Increases of a single element may reflect instability of the ecosystem. If several elements increase simultaneously, this expansion may reflect stable growth of the community.

Reservoirs are connected by pathways which represent real ecosystem processes. Figure 8-1 depicts the biogeochemical reservoirs and pathways of a typical terrestrial ecosystem. Most elements, especially those with no gaseous phase, do not undergo changes in oxidation state and are equally available for exchange between any two reservoirs, provided a pathway exists between the two reservoirs. The chemical environment of the reservoir may, however, regulate the availability of an element by controlling solubility or binding strengths. This condition is especially true for soils.

Ecosystems have boundaries. These boundaries may be as distinct as the border of a pond or as arbitrary as an imaginary circle drawn on a map. Many trace metal studies are conducted in watersheds where some of the boundaries are determined by topography. For atmospheric inputs to terrestrial ecosystems, the boundary is usually defined as the surface of vegetation, exposed rock, or soil. The water surface suffices for aquatic ecosystems.

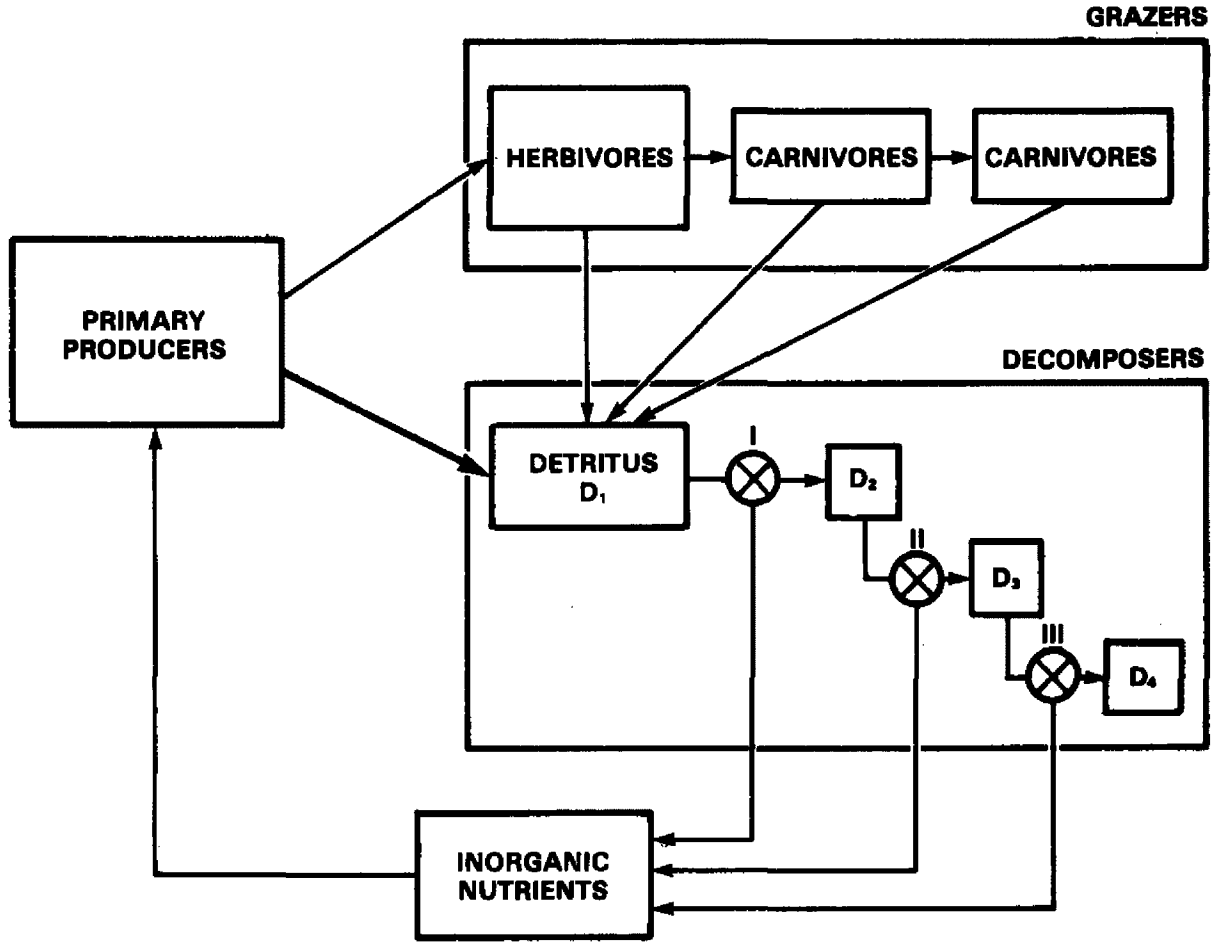

Figure 8-1. This figure depicts cycling processes within the major components of a terrestrial ecosystem, i.e. primary producers, grazers and decomposers. Nutrient and non-nutrient elements are stored in reservoirs within these components. Processes that take place within reservoirs regulate the flow of elements between reservoirs along established pathways. The rate of flow is in part a function of the concentration in the preceding reservoir. Lead accumulates in decomposer reservoirs which have a high binding capacity for this metal. It is likely that the rate of flow away from these reservoirs has increased in past decades and will continue to increase for some time until the decomposer reservoirs are in equilibrium with the entire ecosystem. Inputs to and outputs from the ecosystem as a whole are not shown.

Source: Adapted from Swift et al. (1979).

Non-nutrient elements differ little from nutrient elements in their biogeochemical cycles. Quite often, the cycling patterns are similar to those of a major nutrient. In the case of lead, the reservoirs and pathways are very similar to those of calcium.

The important questions are: Does atmospheric lead interfere with the normal mechanisms of nutrient cycles? How does atmospheric lead influence the normal lead cycle in an ecosystem? Can atmospheric lead interfere with the normal flow of energy through an ecosystem?

8.1.2.3 Biogeochemistry of Lead. Naturally occurring lead from the earth's crust is commonly found in soils and the atmosphere. Lead may enter an ecosystem by weathering of parent rock or by deposition of atmospheric particles. This lead becomes a part of the nutrient medium of plants and the diet of animals. All ecosystems receive lead from the atmosphere. More than 99 percent of the current atmospheric lead deposition is now due to human activities (National Academy of Sciences, 1980). In addition, lead shot from ammunition may be found in many waterways and popular hunting regions, leaded paint chips often occur in older urban regions and lead in fertilizer may contaminate the soil in agricultured regions.

In prehistoric times, the contribution of lead from weathering of soil was probably about 4 g Pb/ha·yr and from atmospheric deposition about 0.02 g Pb/ha·yr, based on estimates of natural and anthropogenic emissions in Chapter 5 and deposition rates discussed in Chapter 6. Weathering rates are presumed to have remained the same, but atmospheric inputs are believed to have increased to 180 g/ha·yr in natural and some cultivated ecosystems, and 3,000 g/ha·yr in urban ecosystems and along roadways (see Chapter 6). In every terrestrial ecosystem of the Northern Hemisphere, atmospheric lead deposition now exceeds weathering by a factor of at least 10, sometimes by as much as 1,000.

Many of the effects of lead on plants, microorganisms, and ecosystems arise from the fact that lead from atmospheric and weathering inputs is retained by soil. Geochemical studies show that less than 3 percent of the inputs to a watershed leave by stream runoff (Siccama and Smith, 1978; Shirahata et al., 1980). In prehistoric times, stream output nearly equalled weathering inputs and the lead content of soil probably remained stable, accumulating at an annual rate of less than 0.1 percent of the original natural lead (reviewed by Nriagu, 1978). Due to human activity, lead in natural soils now accumulates on the surface at an annual rate of 5 to 10 percent of the natural lead. One effect of cultivation is that atmospheric lead is mixed to a greater depth than the 0 to 3 cm of natural soils.

Most of the effects on grazing vertebrates stem from the deposition of atmospheric particles on vegetation surfaces. Atmospheric deposition may occur by either of two mechanisms. Wet deposition (precipitation scavenging through rainout or washout) generally transfers lead directly to the soil. Dry deposition transfers particles to all exposed surfaces. Large particles (>4 μm) are transferred by gravitational mechanisms, small particles (<0.5 μm) are also deposited by wind-related mechanisms.

About half of the foliar dry deposition remains on leaf surfaces following normal rainfall (Elias et al., 1976; Peterson, 1978), but heavy rainfall may transfer the lead to other portions of the plant (Elias and Croxdale, 1980). Koeppe (1981) has reviewed the literature and concluded that less than 1 percent of the surface lead can pass directly into the internal leaf tissues of higher plants. The cuticular layer of the leaves is an effective barrier to aerosol particles and even to metals in solution on the leaf surface (Arvik and Zimdahl, 1974), and passage through the stomata cannot account for a significant fraction of the lead inside leaves (Carlson et al., 1976; 1977).

When particles attach to vegetation surfaces, transfer to soil is delayed from a few months to several years. Due to this delay, large amounts of lead are diverted to grazing food chains, bypassing the soil moisture and plant root reservoirs (Elias et al., 1982).

8.1.3 Criteria for Evaluating Ecosystem Effects

As it is the purpose of this chapter to describe the levels of atmospheric lead that may produce adverse effects in plants, animals, and ecosystems, it is necessary to establish the criteria for evaluating these effects. The first step is to determine the connection between air concentration and ecosystem exposure. If the air concentration is known, ecosystem inputs from the atmosphere can be predicted over time and under normal conditions. These inputs and those from the weathering of soil determine the concentration of lead in the nutrient media of plants, animals, and microorganisms. It follows that the concentration of lead in the nutrient medium determines the concentration of lead in the organism and this in turn determines the effects of lead on the organism.

The fundamental nutrient medium of a terrestrial ecosystem is the soil moisture film which surrounds organic and inorganic soil particles. This film of water is in equilibrium with other soil components and provides dissolved inorganic nutrients to plants. It is chemically different than ground water or rain water and there is little reliable information on the relationship between lead in soil and lead in soil moisture. Thus, it appears impossible to quantify all the steps by which atmospheric lead is transferred to plants. Until more information is available on lead in soil moisture, another approach may be more productive. This involves determining the degree of contamination of organisms by comparing the present known concentrations with calculated prehistoric concentrations.

Prehistoric concentrations of lead have been calculated for only a few types of organisms. However, the results are so low that any normal variation, even of an order of magnitude, would not seriously alter the degree of contamination. The link between lead in the prehistoric atmosphere and in prehistoric organisms may allow us to predict concentrations of lead in organisms based on present or future concentrations of atmospheric lead.

It is reasonable to infer a relationship between degree of contamination and physiological effect. It seems appropriate to assume that natural levels of lead which were safe for organisms in prehistoric times would also be safe today. It is also reasonable that some additional atmospheric lead can be tolerated by all populations of organisms with no ill effects, that some populations are more tolerant than others, and that some individuals within populations are more tolerant of lead effects than others.

For nutrient elements, the concept of tolerance is not new. The Law of Tolerance (illustrated in Figure 8-2) states that any nutrient may be present at concentrations either too low or too high for a given population and that the ecological success of a population is greatest at some optimum concentration of the nutrient (Smith, 1980, p. 35). In a similar manner, the principle applies to non-nutrient elements. Although there is no minimum concentration below which the population cannot survive, there is a concentration above which the success of the population will decline (point of initial response) and a concentration at which the entire population will die (point of absolute toxicity). In this respect, both nutrients and non-nutrients behave in a similar manner at concentrations above some optimum.

Certain variables make the points of initial response and absolute toxicity somewhat imprecise. The point of initial response depends on the type of response investigated. This response may be at the molecular, tissue, or organismic level, with the molecular response occurring at the lowest concentration. Similarly, at the point of absolute toxicity, death may occur instantly at high concentrations or over a prolonged period of time at somewhat lower concentrations. Nevertheless, the gradient between these two points remains an appropriate basis on which to evaluate known environmental effects, and any information which correctly positions this part of the tolerance curve will be of great value.

The normal parameters of a tolerance curve, i.e., concentration and ecological success, can be replaced by degree of contamination and percent physiological dysfunction, respectively (Figure 8-3). Use of this method of expressing degree of contamination should not imply that natural levels are the only safe levels. It is likely that some degree of contamination can be tolerated with no physiological effect.

Data reported by the National Academy of Sciences (1980) are used to determine the typical natural lead concentrations shown in various compartments of ecosystems in Table 8-1. These data are from a variety of sources and are simplified to the most probable value within the range reported by NAS. The actual prehistoric air concentration was probably near the low end of the range (0.02-1.0 ng/m^3), as present atmospheric concentrations of 0.3 ng/m^3 in the Southern Hemisphere and 0.07 ng/m^3 at the South Pole (Chapter 5), would seem to preclude natural lead values higher than this.

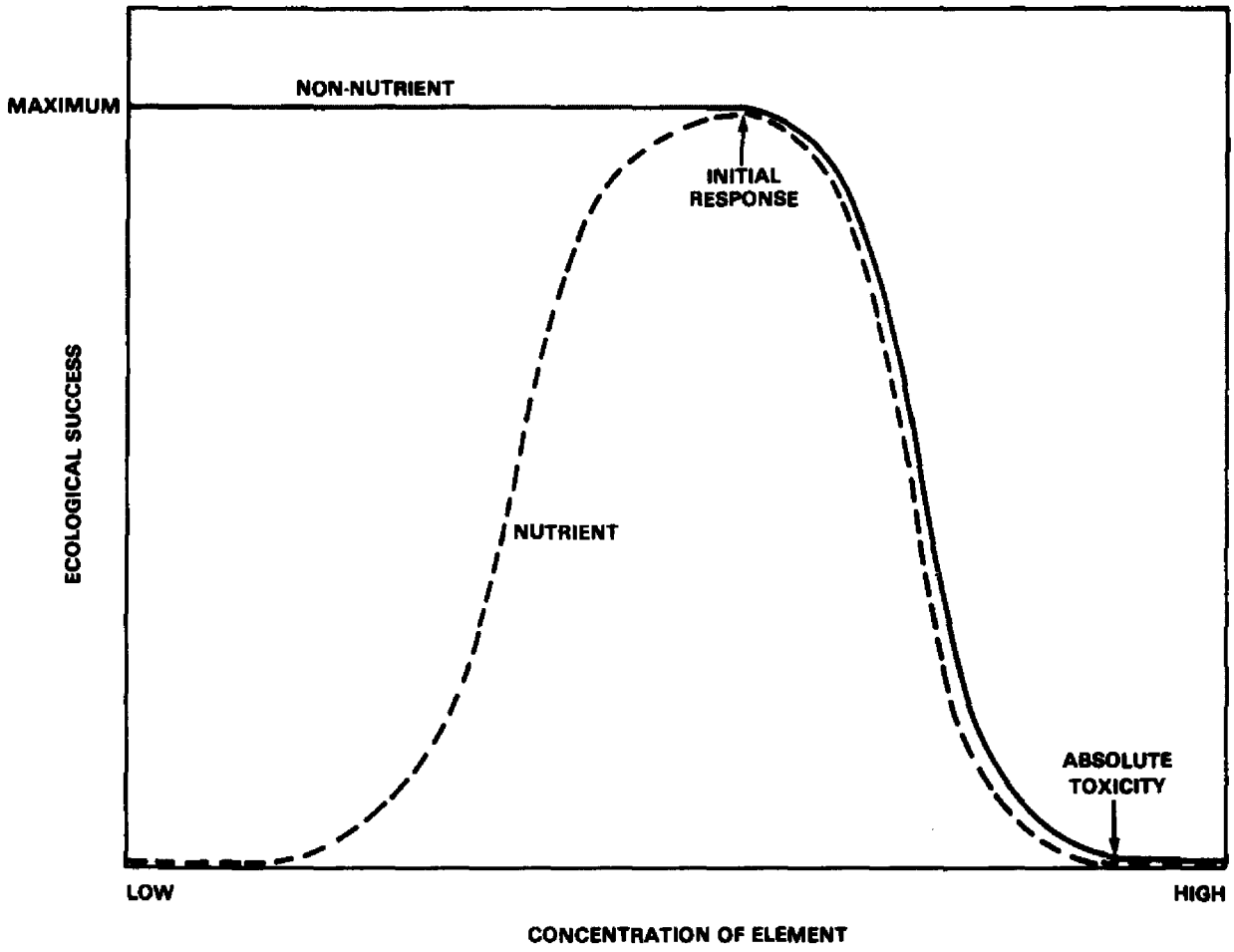

Figure 8-2. The ecological success of a population depends in part on the availability of all nutrients at some optimum concentration. The dashed line of this diagram depicts the rise and decline of ecological success (the ability of a population to grow, survive and reproduce) over a wide concentration range of a single element. The curve need not be symmetrically bell-shaped, but may be skewed to the right or left. Although the range in concentration that permits maximum success may be much wider than shown here, the important point is that at some high concentration, the nutrient element becomes toxic. The tolerance of populations for high concentrations of non-nutrients (solid line) is similar to that of nutrients, although there is not yet any scientific basis for describing the exact shape of this portion of the curve.

Source: Adapted from Smith (1980).

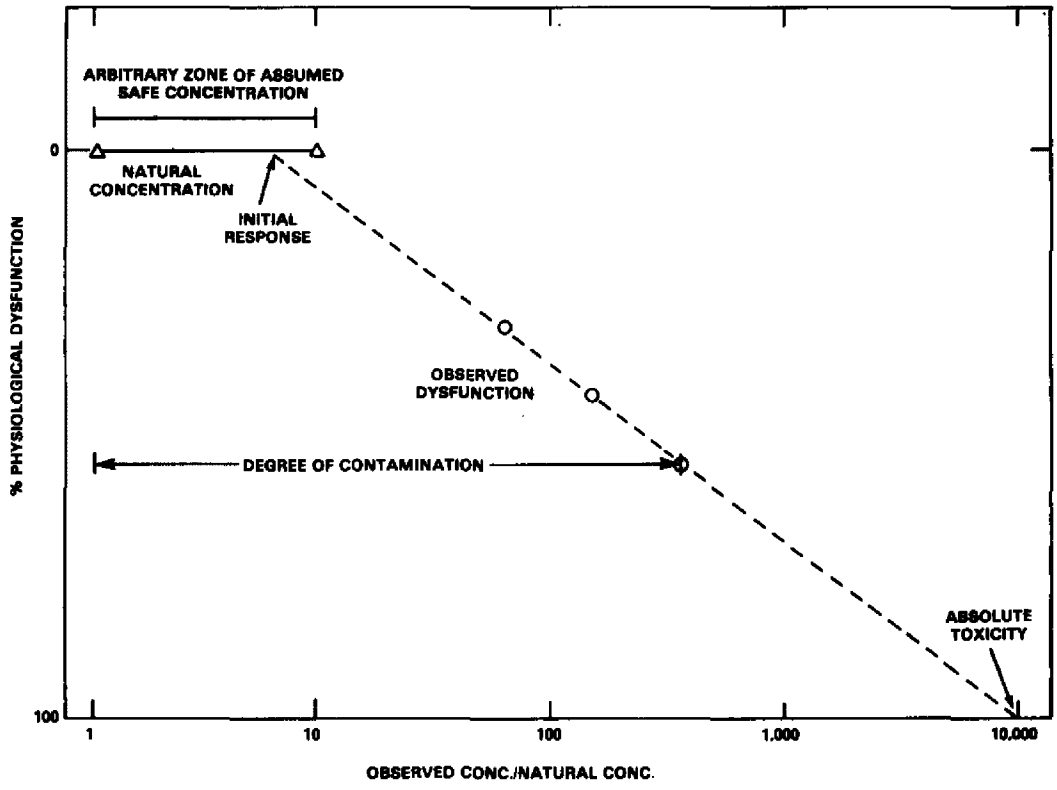

Figure 8-3. This figure attempts to reconstruct the right portion of a tolerance curve, similar to Figure 8-2 but plotted on a semilog scale, for a population using a limited amount of information. If the natural concentration is known for a population and if it is arbitrarily assumed that 10x natural concentration is also safe, then the zone of assumed safe concentration defines the region.

TABLE 8-1. ESTIMATED NATURAL LEVELS OF LEAD IN ECOSYSTEMS

Component	Range	Best estimate
Air	0.01-1.0 ng/m^3	0.07
Soil		
Inorganic	5-25 µg/g	12.0
Organic	1 µg/g	1.0
Soil moisture	0.0002 µg/g	0.0002
Plant leaves	0.01-0.1 µg/g dw	0.05
Herbivore bones	0.04-0.12 µg/g dw	0.12
Carnivore bones	0.01-0.03 µg/g dw	0.03

Source: Ranges are from the National Academy of Sciences, (1980); best estimates are discussed in the text. Units for best estimates are the same as for ranges.

In prehistoric times, the rate of entry of lead into the nutrient pool available to plants was predominantly determined by the rate of weathering of inorganic minerals in fragments of parent rock material. Geochemical estimates of denudation and adsorption rates (Chapter 6) suggest a median value of 12 µg/g as the average natural lead content of total soil, with the concentration in the organic fraction at approximately 1 µg/g.

Studies have shown the lead content of leafy vegetation to be 90 percent anthropogenic, even in remote areas (Crump and Barlow, 1980; Elias et al., 1976, 1978). The natural lead content of nuts and fruits may be somewhat higher than leafy vegetation, based on internal lead concentrations of modern samples (Elias et al., 1982). The natural lead concentrations of herbivore and carnivore bones were reported by Elias et al. (Elias and Patterson, 1980; Elias et al., 1982). These estimates are based on predicted Pb/Ca ratios calculated from the observed biopurification of calcium reservoirs with respect to Sr, Ba, and Pb, on the systematic evaluation of anthropogenic lead inputs to the food chain (Section 8.5.3), and on measurements of prehistoric mammalian bones.

8.2 LEAD IN SOILS AND SEDIMENTS

8.2.1 Distribution of Lead in Soils

Because lead in soil is the source of most effects on plants, microorganisms, and ecosystems, it is important to understand the processes that control the accumulation of lead in soil. The major components of soil are: 1) fragments of inorganic parent rock material; 2) secondary inorganic minerals; 3) organic constituents, primarily humic substances, which are residues of decomposition or products of decomposer organisms; 4) Fe-Mn oxide films, which coat the surfaces of all soil particles and appear to have a high binding capacity for metals; 5) soil microorganisms, most commonly bacteria and fungi, although protozoa and soil algae may also be found; and 6) soil moisture, the thin film of water surrounding soil particles which is the nutrient medium of plants. Some watershed studies consider that fragments of inorganic parent rock material lie outside the forest ecosystem, because transfer from this compartment is so slow that much of the material remains inert for centuries.

The concentration of lead ranges from 5 to 30 µg/g in the top 5 cm of most soils not adjacent to sources of industrial lead, although 5 percent of the soils contain as much as 800 µg/g (Chapter 5). Aside from surface deposition of atmospheric particles, plants in North America average about 0.5 to 1 µg/g dw (Peterson, 1978) and animals roughly 2 µg/g (Forbes and Sanderson, 1978). Thus, soils contain the greater part of total ecosystem lead. In soils, lead in parent rock fragments is tightly bound within the crystalline structures of the inorganic soil minerals. It is released to the ecosystem only by surface contact with soil moisture films.

Hutchinson (1980) has reviewed the effects of acid precipitation on the ability of soils to retain cations. Excess calcium and other metals are leached from the A horizon of soils by rain with a pH more acidic than 4.5. Most soils in the eastern United States are normally acidic (pH 3.5 to 5.2) and the leaching process is a part of the complex equilibrium maintained in the soil system. By increasing the leaching rate, acid rain can reduce the availability of nutrient metals to organisms dependent on the top layer of soil. Tyler (1978) reports the effect of acid rain on the leaching rate (reported as residence time) for lead and other metals. Simulated rain of pH 4.2 to 2.8 showed the leaching rate for lead increases with decreasing pH, but not nearly as much as that of other metals, especially Cu, Mn, and Zn. This would be as expected from the high stability constant of lead relative to other metals in humic acids (see Section 6.5.1). It appears from this limited information that acidification of soil may increase the rate of removal of lead from the soil, but not before several major nutrients are removed first. The effect of acid rain on the retention of lead by soil moisture is not known.

8.2.2 Origin and Availability of Lead in Aquatic Sediments

Atmospheric lead may enter aquatic ecosystems by wet or dry deposition (Dolske and Sievering, 1979) or by the erosional transport of soil particles (Baier and Healy, 1977). In waters not polluted by industrial, agricultural, or municipal effluents, the lead concentration is usually less than 1 µg/l. Of this amount, approximately 0.02 µg/l is natural lead and the rest is anthropogenic lead, probably of atmospheric origin (Patterson, 1980). Surface waters mixed with urban effluents may frequently reach lead concentrations of 50 µg/l, and occasionally higher (Bradford, 1977).

In aqueous solution, virtually all lead is divalent, as tetravalent lead can exist only under extremely oxidizing conditions (reviewed by Rickard and Nriagu, 1978; Chapter 3). At pH higher than 5, divalent lead can form a number of hydroxyl complexes, most commonly $PbOH^+$, $Pb(OH)_2$, and $Pb(OH)_3^-$. At pH lower than 5, lead exists in solution as hydrated Pb. In still water, lead is removed from the water column by the settling of lead-containing particulate matter, by the formation of insoluble complexes, or by the adsorption of lead onto suspended organic particles. The rate of sedimentation is determined by temperature, pH, oxidation-reduction potential, ionic competition, the chemical form of lead in water, and certain biological activities (Jenne and Luoma, 1977). McNurney et al. (1977) found 14 µg Pb/g in stream sediments draining cultivated areas and 400 µg/g in sediments associated with urban ecosystems. Small sediment grain size and high organic content contributed to increased retention in sediments.

8.3 EFFECTS OF LEAD ON PLANTS

8.3.1 Effects on Vascular Plants and Algae

Some physiological and biochemical effects of lead on vascular plants have been detected under laboratory conditions at concentrations higher than normally found in the environment. The commonly reported effects are the inhibition of photosynthesis, respiration or cell elongation, all of which reduce the growth of the plant (Koeppe, 1981). Lead may also induce premature senescence, which may affect the long-term survival of the plant or the ecological success of the plant population. To provide a meaningful evaluation of these effects, it is necessary to examine the correlation between laboratory conditions and typical conditions in nature with respect to form, concentration, and availability of lead. First, the reader must understand what is known of the movement of lead from soil to the root to the stem and finally to the leaf or flower. Most notably, there are specific barriers to lead at the soil:soil moisture interface and at the root:shoot interface which retard the movement of lead and reduce the impact of lead on photosynthetic and meristematic (growth and reproduction) tissue.

8.3.1.1 Uptake by Plants. Most of the lead in or on a plant occurs on the surfaces of leaves and the trunk or stem. The surface concentration of lead in trees, shrubs, and grasses exceeds the internal concentration by a factor of at least five (Elias et al, 1978). There is little or no evidence of lead uptake through leaves or bark. Foliar uptake, if it does occur, cannot account for more than 1 percent of the uptake by roots, and passage of lead through bark tissue has not been detected (Arvik and Zimdahl, 1974; reviewed by Koeppe, 1981; Zimdahl, 1976). Krause and Kaiser (1977) were able to show foliar uptake and translocation of lead mixed with cadmium, copper, and manganese oxides when applied in large amounts (122 mg/m^2) directly to leaves. This would be comparable to 100,000 days accumulation at a remote site (0.12 $ng/cm^2 \cdot d$) (Elias et al., 1978). The uptake of lead was less than that of other metals and application of sulfur dioxide did not increase the foilar uptake of these metals. The major effect of surface lead at ambient concentrations seems to be on subsequent components of the grazing food chain (Section 8.4.1) and on the decomposer food chain following litterfall (Elias et al., 1982). (See also Section 8.4.2.)

Uptake by roots is the only major pathway for lead into plants. The amount of lead that enters plants by this route is determined by the availability of lead in soil, with apparent variations according to plant species. Soil cation exchange capacity, a major factor, is determined by the relative size of the clay and organic fractions, soil pH, and the amount of Fe-Mn oxide films present (Nriagu, 1978). Of these, organic humus and high soil pH are the dominant factors in immobilizing lead (Chapter 6). Under natural conditions, most of the total lead in soil would be tightly bound within the crystalline structure of inorganic soil fragments, unavailable to soil moisture. Available lead, bound on clays, organic colloids,

and Fe-Mn films, would be controlled by the slow release of bound lead from inorganic rock sources. Since before 3000 B.C., atmospheric lead inputs through litter decomposition have increased the pool of available lead bound on organic matter within the soil reservoir (see Section 5.1).

Because lead is strongly immobilized by humic substances, only a small fraction (perhaps 0.01 percent in soils with 20 percent organic matter, pH 5.5) is released to soil moisture (see Chapter 6). In soil moisture, lead may pass along the pathway of water and nutrient uptake on either a cellular route through the cell membranes of root hairs (symplastic route) or an extracellular route between epidermal cells into the intercellular spaces of the root cortex (apoplastic route) (Foy et al., 1978). Lead probably passes into the symplast by membrane transport mechanisms similar to the uptake of calcium or other bivalent cations.

At 500 µg Pb/g nutrient solution, lead has been shown to accumulate in the cell walls of germinating Raphinus sativus roots (Lane and Martin, 1982). This concentration is much higher than that found by Wong and Bradshaw (1982) to cause inhibition of germinating root elongation (less than 2.5 µg/g), absence of root growth (5 µg/g), or 55 percent inhibition of seed germination (20 to 40 µg/g) in the rye grass, Colium perenne. Lane and Martin (1982) also observed lead in cytoplasmic organelles which appeared to have a storage function because of their osmiophillic properties. It was suggested that the organelles eventually emptied their contents into the tonoplast.

The accumulation of lead in cell walls and cytoplasmic bodies has also been observed in blue green algae by Jensen et al. (1982), who used X-ray energy dispersive analysis in conjunction with scanning electron microscopy to observe high concentrations of lead and other metals in these single celled procaryotic organisms. They found the lead concentrated in the third of the four layered cell wall and in polyphosphate bodies (not organelles, since they are not membrane-bound) which appeared to be a storage site for essential metals. The nutrient solution contained 100 µg Pb/g. The same group (Rachlin et al., 1982) reported morphological changes in the same blue green alga (Plectonema boryanum). There was a significant increase in cell size caused by the lead, which indicated that the cell was able to detoxify its cytoplasm by excreting lead with innocuous cell wall material.

It appears that two defensive mechanisms may exist in the roots of plants for removing lead from the stream of nutrients flowing to the above ground portions of plants. Lead may be deposited with cell wall material exterior to the individual root cells, or may be sequestered in organelles within the root cells. Any lead not captured by these mechanisms would likely move with nutrient metals cell-to-cell through the symplast and into the vascular system.

Uptake of lead by plants may be enhanced by symbiotic associations with mycorrhizal fungi The three primary factors that control the uptake of nutrients by plants are the surface area

of the roots, the ability of the root to absorb particular ions, and the transfer of ions through the soil. The symbiotic relationship between mycorrhizal fungi and the roots of higher plants can increase the uptake of nutrients by enhancing all three of these factors (Voigt, 1969). The typical ectomycorrhiza consists of a mantle or sheath of mycelia that completely surrounds the root. The physical extension of the sheath may increase the volume of the root two to three times (Voigt, 1969). Mycorrhizal roots often show greater affinities for nutrients than do uninfected roots of the same species grown in the same conditions. In many soil systems, where the bulk of the nutrients are bound up in parent rock material, efficient uptake of these nutrients by plants depends on the ability of organisms in the rhizosphere (plant roots, soil fungi, and bacteria) to increase the rates of weathering. Mycorrhizal fungi are known to produce and secrete into their environment many different acidic compounds (e.g., malic and oxalic acids). In addition, mycorrhizal roots have been shown to release more carbon dioxide into the rhizosphere than do non-mycorrhizal roots as a result of their increased rates of respiration. Carbon dioxide readily combines with soil moisture to produce carbonic acid. All of these acids are capable of increasing the weathering rates of soil particles such as clays, and altering the binding capacity of organic material, thereby increasing the amount of nutrients in the soil solution. Mycorrhizae are known to enhance the uptake of zinc by pine roots (Bowen et al., 1974), and it is likely that lead uptake is similarly increased, by inference to the ability of mycorrhizae to enhance the uptake of calcium by pine roots (Melin and Nilsson, 1955; Melin et al., 1958).

The translocation of lead to aboveground portions of the plant is not clearly understood. Lead may follow the same pathway and be subject to the same controls as a nutrient metal such as calcium. This assumption implies that the plant root has no means of discriminating against lead during the uptake process, and it is not known that any such discrimination mechanism exists. There may be several mechanisms, however, that excrete lead back out of the root or that prevent its translocation to other plant parts. The primary mechanisms may be storage in cell organelles or adsorption on cell walls. The apoplast contains an important supply of plant nutrients, including water. Lead in the apoplast remains external to the cells and cannot pass to vascular tissue without at least passing through the cell membranes of the endodermis. Because this extracellular region is bounded on all sides by cell walls, the surface of which is composed of layers of cellulose strands, the surface area of the apoplast is comparable to a sponge. It is likely that much of the lead in roots is adsorbed to the apoplast surface. Dictyosomes, cytoplasmic organelles which contain cell wall material, may carry lead from inside the cell through the membrane to become a part of the external cell wall (Malone et al., 1974), possibly replacing calcium in calcium pectate. Lead may also be stored and excreted as lead phosphate in dictyosome vesicles (Malone et al.,

1974). Nevertheless, some lead does pass into the vascular tissue, along with water and dissolved nutrients, and is carried to physiologically active tissue of the plant.

Evidence that lead in contaminated soils can enter the vascular system of plants and be transported to aboveground parts may be found in the analysis of tree rings. Rolfe (1974) found four-fold increases in both rural and urban trees using 10 year increments of annual rings for the period 1910-20 and comparing these to annual rings of the period 1963-73. Symeonides (1979) found a two-fold increase from 1907-17 to 1967-77 in trees at a high-lead site, with no increase in trees from a low-lead site. Finally, Baes and Ragsdale (1981), using only ring porous species, found significant post-1930 increases in Quercus and Carya with high lead exposure, but only in Carya with low lead exposure. These chronological records confirm that lead can be translocated from roots to the upper portions of the plant and that the amounts translocated are in proportion to the concentrations of lead in soil.

8.3.1.2 Physiological Effects on Plants. Because most of the physiologically active tissue of plants is involved in growth, maintenance, and photosynthesis, it is expected that lead might interfere with one or more of these processes. Indeed, such interferences have been observed in laboratory experiments at lead concentrations greater than those normally found in the field, except near smelters or mines (Koeppe, 1981). It is likely that more is known of these effects because these are the physiological processes studied more vigorously than others. Studies of other plant processes, especially maintenance, flowering, and hormone development, have not been conducted and no conclusion can be reached concerning possible lead effects on these processes.

Inhibition of photosynthesis by lead may be by direct interference with the light reaction or the indirect interference with carbohydrate synthesis. At 21 μg Pb/g reaction solution, Miles et al. (1972) demonstrated substantial inhibition of photosystem II near the site of water splitting, a biochemical process believed to require manganese. Homer et al. (1979) found a second effect on photosystem II at slightly higher concentrations of lead. This effect was similar to that of DCMU [3-(3,4-dichlorophenyl)-1,1-dimethylurea], a reagent commonly used to uncouple the photosynthetic electron transport system. Bazzaz and Govindjee (1974) suggested that the mechanism of lead inhibition was a change in the conformation of the thylakoid membranes, separating and isolating pigment systems I and II. Wong and Govindjee (1976) found that lead also interferes with P700 photooxidation and re-reduction, a part of the photosystem I light reaction. Homer et al. (1981) found a lead tolerant population of the grass Phalaris arundinacea had lowered the ratio of chlorophyll a/chlorophyll b, believed to be a compensation for photosystem II inhibition. There was no change in the total amount of chlorophyll, but the mechanism of inhibition was considered different than that of Miles et al. (1972). Hampp and Lendzian (1974) found that lead chloride inhibits the synthesis of

chlorophyll b more than that of chlorophyll a at concentrations up to 100 mg Pb/g. Devi Prasad and Devi Prasad (1982) found 10 percent inhibition of pigment production in three species of green algae at 1 µg/g, increasing to 50 percent inhibition at 3 µg/g. Bazzaz et al. (1974, 1975) observed reduced net photosynthesis which may have been caused indirectly by inhibition of carbohydrate synthesis. Without carbohydrates, stomatal guard cells remain flaccid, transpiration ceases, carbon dioxide fixation decreases, and further carbohydrate synthesis is inhibited.

The stunting of plant growth may be by the inhibition of the growth hormone IAA (indole-3-ylacetic acid). Lane et al. (1978) found a 25 percent reduction in elongation at 10 µg/g lead as lead nitrate in the nutrient medium of wheat coleoptiles. This effect could be reversed with the addition of calcium at 18 µg/g. Lead may also interfere with plant growth by reducing respiration or inhibiting cell division. Miller and Koeppe (1970) and Miller et al. (1975) showed succinate oxidation inhibition in isolated mitochondria as well as stimulation of exogenous NADH oxidation with related mitochondrial swelling. Hassett et al. (1976), Koeppe (1977), and Malone et al. (1978) described significant inhibition of lateral root initiation in corn. Inhibition increased with the simultaneous addition of cadmium.

Sung and Yang (1979) found that lead at 1 µg/g can complex with and inactivate ATPase to reduce the production and utilization of ATP in kidney bean (Phaseolus vulgaris) and buckwheat leaves (Fagopyrum esculentum). The lead was added hydroponically at concentrations up to 1,000 µg/g. Kidney bean ATPase showed a continued response from 1 to 1,000 µg/g, but buckwheat leaves showed little further reduction after 10 µg/g. Neither extracted ATP nor chemically added ATP could be used by the treated plants. Lee et al. (1976) found a 50 percent increase in the activity of several enzymes related to the onset of senescence in soybean leaves when lead was added hydroponically at 20 µg/g. These enzymes were acid phosphatase, peroxidase, and alpha-amylase. A build-up of ammonia was observed along with a reduction in nitrate, calcium, and phosphorus. Glutamine synthetase activity was also reduced by 65 percent. Continued increases in effects were observed up to 100 µg/g, including a build-up of soluble protein. Päivöke (1979) also observed a 60 percent increase in acid phosphatase activity during the first 6 days of pea seedling germination (Pisum sativum) at 2 µg/g, under low nutrient conditions. The accumulation of soluble protein was observed and the effect could be reversed with the addition of nutrients, including calcium.

The interaction of lead with calcium has been shown by several authors, most recently by Garland and Wilkins (1981), who demonstrated that barley seedlings (Hordeum vulgare), which were growth inhibited at 2 µg Pb/g sol. with no added calcium, grew at about half the control rate with 17 µg Ca/g sol. This relation persisted up to 25 µg Pb/g sol. and 500 µg Ca/g sol.

These studies of the physiological effects of lead on plants all show some effect at concentrations from 2 to 10 μg/g in the nutrient medium of hydroponically-grown agricultural plants. It is certain that no effects would have been observed at these concentrations had the lead solutions been added to normal soil, where the lead would have been bound by humic substances. There is no firm relationship between soil lead and soil moisture lead, because each soil type has a unique capacity to retain lead and to release that lead to the soil moisture film surrounding the soil particle. Once in soil moisture, lead seems to pass freely to the plant root according to the capacity of the plant root to absorb water and dissolved substances (Koeppe, 1981).

Chapter 6 discusses the many parameters controlling the release of lead from soil to soil moisture, but so few data are available on observed lead concentrations in soil moisture that no model can be formed. It seems reasonable that there may be a direct correlation between lead in hydroponic media and lead in soil moisture. Hydroponic media typically have an excess of essential nutrients, including calcium and phosphorus, so that movement of lead from hydroponic media to plant root would be equal to or slower than movement from soil moisture to plant root. Hughes (1981) adopted the general conclusion that extractable soil lead is typically 10 percent of total soil lead. However, this lead was extracted chemically under laboratory conditions more rigorous than the natural equilibrium between soil and soil moisture. Ten percent should therefore be considered the upper limit, where the ability of soil to retain lead is at a minimum. A lower limit of 0.01 percent is based on the only known report of lead in both soil and soil moisture (16 μg/g soil, 1.4 μg/g soil moisture; Elias et al., 1982). This single value shows neither trends with different soil concentrations nor the soil component (organic or inorganic) that provides the lead to the soil moisture. But the number (0.01 percent) is a conservative estimate of the ability of soil to retain lead, since the conditions (pH, organic content) were optimum for retaining lead. A further complication is that atmospheric lead is retained at the surface (0-2 cm) of the soil profile (Martin and Coughtrey, 1981), whereas most reports of lead in soil pertain to samples from 0 to 10 cm as the "upper" layer of soil. Any plant that absorbs solely from the top few centimeters of soil obviously is exposed to more lead than one with roots penetrating to a depth of 25 cm or more. Agricultural practices that cultivate soil to a depth of 25 cm blend in the upper layers with lower to create a soil with average lead content somewhat above background.

These observations lead to the general conclusion that even under the best of conditions where soil has the highest capacity to retain lead, most plants would experience reduced growth rate (inhibition of photosynthesis, respiration, or cell elongation) in soils of 10,000 μg Pb/g or greater. Concentrations approaching this value typically occur around smelters (Martin and Coughtrey, 1981) and near major highways (Wheeler and Rolfe, 1979). These con-

clusions pertain to soil with the ideal composition and pH to retain the maximum amount of lead. Acid soils or soils lacking organic matter would inhibit plants at much lower lead concentrations.

The rate at which atmospheric lead accumulates in soil varies from 1.1 $mg/m^2 \cdot yr$ average global deposition (Table 6-7) to 3,000 $mg/m^2 \cdot yr$ near a smelter (Patterson et al., 1975). Assuming an average density of 1.5 g/cm^3, undisturbed soil to a depth of 2 cm (20,000 cm^3/m^2) would incur an increase in lead concentration at a rate of 0.04 to 100 µg/g soil·yr. This means remote or rural area soils may never reach the 10,000 µg/g threshold but that undisturbed soils closer to major sources may be within range in the next 50 years.

8.3.1.3 Lead Tolerance in Vascular Plants. Some plant species have developed populations tolerant to high lead soils (Antonovics et al., 1971). In addition to Homer et al. (1981) cited above, Jowett (1964) found populations of Agrostis tenuis in pure stands on acidic spoil banks near an abandoned mine. The exclusion of other species was attributed to root inhibition. Populations of A. tenuis from low-lead soils had no tolerance for the high lead soils. Several other studies suggest that similar responses may occur in populations growing in lead-rich soils (reviewed in Peterson, 1978). A few have suggested that crops may be cultivated for their resistance to high lead soils (Gerakis et al., 1980; John, 1977).

Using populations taken from mine waste and uncontaminated control areas, some authors have quantified the degree of tolerance of Agrostis tenuis (Karataglis, 1982) and Festuca rubra (Wong, 1982) under controlled laboratory conditions. Root elongation was used as the index of tolerance. At 36 µg Pb/g nutrient solution, all populations of A. tenuis were completely inhibited. At 12 µg Pb/g, the control populations from low lead soils were completely inhibited, but the populations from mine soils achieved 30 percent of their normal growth (growth at no lead in nutrient solution). At 6 µg/g, the control populations achieved 10 percent of their normal growth, tolerant populations achieved 42 percent. There were no measurements below 6 µg/g. Wong (1982) measured the index of tolerance at one concentration only, 2.5 µg Pb/g nutrient solution, and found that non-adapted populations of Festuca rubra which had grown on soils with 47 µg/g total lead content were completely inhibited, populations from soils with 350 to 650 µg/g achieved 3 to 7 percent of normal growth, and populations from 5,000 µg/g soil achieved nearly 40 percent of normal growth.

These studies support the conclusion that inhibition of plant growth begins at a lead concentration of less than 1 µg/g soil moisture and becomes completely inhibitory at a level between 3 and 10 µg/g. Plant populations that are genetically adapted to high lead soils may achieve 50 percent of their normal root growth at lead concentrations above 3 µg/g. These experiments did not show the effect of reduced root growth on total productivity, but they did show that exposure to high lead soils is a requirement for genetic adaptation and that, at

least in the case of F. rubra, plant lead concentrations increase with increasing concentrations in the soil.

8.3.1.4 Effects of Lead on Forage Crops. In the 1977 Criteria Document (U.S. Environmental Protection Agency, 1977), there was a general awareness that most of the lead in plants was surface lead from the atmosphere. Most studies since then have addressed the problem of distinguishing between surface and internal plant lead. The general conclusion is that, even in farmlands remote from major highways or industrial sources, 90 to 99 percent of the total plant lead is of anthropogenic origin (National Academy of Sciences, 1980). Obviously, the critical agricultural problem concerns forage crops and leafy vegetables. In Great Britain, Crump and Barlow (1982) determined that within 50 m of the highway, surface deposition is the major source of lead in forage vegetation. Beyond this range, seasonal effects can obscure the relative contribution of atmospheric lead. The atmospheric deposition rate appears to be much greater in the winter than in the summer. Two factors may explain this difference. First, deposition rate is a function of air concentration, particle size distribution, windspeed, and surface roughness. Of these, only particle size distribution is likely to be independent of seasonal effects. Lower windspeeds or air concentration during the summer could account for lower deposition rates. Second, it may be that the deposition rate only appears to change during the summer. With an increase in biomass and a greater turnover in biomass, the effective surface area increases and the rate of deposition, which is a function of surface area, decreases. During the summer, lead may not build up on the surface of leaves as it does in winter, even though the flux per unit of ground area may be the same.

8.3.1.5 Summary of Plant Effects. When soil conditions allow lead concentrations in soil moisture to exceed 2 to 10 µg/g, most plants experience reduced growth due to the inhibition of one or more physiological processes. Excess calcium or phosphorus may reverse the effect. Plants that absorb nutrients from deeper soil layers may receive less lead. Acid rain is not likely to release more lead until after major nutrients have been depleted from the soil. A few species of plants have the genetic capability to adapt to high lead soils.

8.3.2 Effects on Bacteria and Fungi

8.3.2.1 Effects on Decomposers. Tyler (1972) explained three ways in which lead might interfere with the normal decomposition processes in a terrestrial ecosystem. Lead may be toxic to specific groups of decomposers, it may deactivate enzymes excreted by decomposers to break down organic matter, or it may bind with the organic matter to render it resistant to the action of decomposers. Because lead in litter may selectively inhibit decomposition by soil bacteria at 2,000 to 5,000 µg/g (Smith, 1981, p. 160), forest floor nutrient cycling processes may be seriously disturbed near lead smelters (Bisessar, 1982; Watson et al., 1976). This is

especially important because approximately 70 percent of plant biomass enters the decomposer food chain (Swift et al., 1979, p. 6). If decomposition of the biomass is inhibited, then much of the energy and nutrients remain unavailable to subsequent components of the food chain. There is also the possibility that the ability of soil to retain lead would be reduced, as humic substances are byproducts of bacterial decomposition.

During decomposition, plant tissues are reduced to resistant particulate matter, as soluble organic and inorganic compounds are removed by the chemical action of soil moisture and the biochemical action of microorganisms (Odum and Drifmeyer, 1978). Each group of microorganisms specializes in the breakdown of a particular type of organic molecule. Residual waste products of one group become the food for the next group. Swift et al. (1979, p. 101) explained this relationship as a cascade effect with the following generalized pattern (Figure 8-4). Organisms capable of penetrating hard or chemically resistant plant tissue are the primary decomposers. These saprotrophs, some of which are fungi and bacteria that reside on leaf surfaces at the initial stages of senescence, produce a wide range of extracellular enzymes. Others may reside in the intestinal tract of millipedes, beetle larvae, and termites capable of mashing plant tissue into small fragments. The feces and remains of this group and the residual plant tissue are consumed by secondary decomposers, i.e., the coprophilic fungi, bacteria, and invertebrates (including protozoa) specialized for consuming bacteria. These are followed by tertiary decomposers. Microorganisms usually excrete enzymes that carry out this digestive process external to their cells. They are often protected by a thick cell coat, usually a polysaccharide. Because they are interdependent, the absence of one group in this sequence seriously affects the success of subsequent groups, as well as the rate at which plant tissue decomposes. Each group may be affected in a different way and at different lead concentrations. Lead concentrations toxic to decomposer microbes may be as low as 1 to 5 µg/g or as high as 5,000 µg/g (Doelman, 1978).

Under conditions of mild contamination, the loss of one sensitive bacterial population may result in its replacement by a more lead-tolerant strain. Inman and Parker (1978) found that litter transplanted from a low-lead to a high-lead site decayed more slowly than high-lead litter, suggesting the presence of a lead sensitive microorganism at the low-lead site. When high-lead litter was transplanted to the low-lead site, decomposition proceeded at a rate faster than the low-lead litter at the low-lead site. In fact, the rate was faster than the high-lead litter at the high-lead site, suggesting even the lead tolerant strains were somewhat inhibited. The long term effect is a change in the species composition of the ecosystem, which will be considered in greater detail in Section 8.5.2.

Delayed decomposition has been reported near smelters (Jackson and Watson, 1977), mine waste dumps (Williams et al., 1977), and roadsides (Inman and Parker, 1978). This delay is

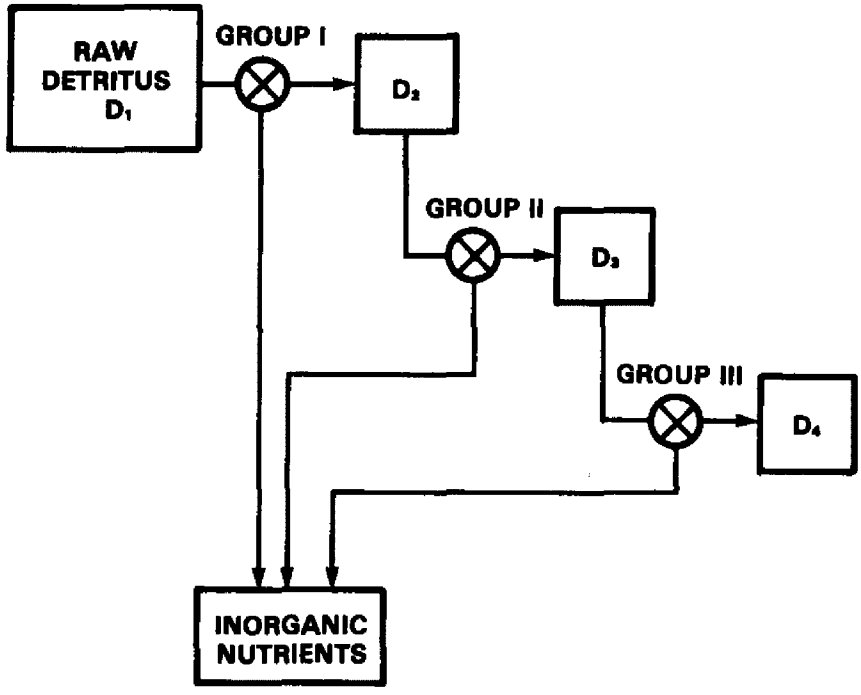

Figure 8-4. Within the decomposer food chain, detritus is progressively broken down in a sequence of steps regulated by specific groups of decomposers. Because of the cascade effect of this process, the elimination of any decomposer interrupts the supply of organic nutrients to subsequent groups and reduces the recycling of inorganic nutrients to plants. Undecomposed litter would accumulate at the stages preceding the affected decomposer.

Source: Adapted from Swift et al. (1979).

generally in the breakdown of litter from the first stage (O_1) to the second (O_2) with intact plant leaves and twigs accumulating at the soil surface. The substrate concentrations at which lead inhibits decomposition appear to be very low. Williams et al. (1977) found inhibition in 50 percent of the bacteria and fungal strains at 50 µg Pb/ml nutrient solution. The community response time for introducing lead tolerant populations seems very fast, however. Doelman and Haanstra (1979a,b) found lead-tolerant strains had replaced non-tolerant bacteria within 3 years of lead exposure. These new bacteria were predominately thick-coated gram negative strains and their effectiveness in replacing lead-sensitive strains was not evaluated in terms of soil decomposition rates.

Tyler (1982) has also shown that many species of wood-decaying fungi do not accumulate Pb, Ca, Sr, or Mn as strongly as they do other metals, even the normally toxic metal, cadmium.

Accumulation was expressed as the ratio of the metal concentration in the fungus to its substrate. A ratio of greater than one implies accumulation, less than one, exclusion. Of 11 species, manganese was excluded by ten, strontium by nine, lead by eight, and calcium by seven. Potassium, at the other end of the spectrum, was not excluded by any species. The species which appeared to accumulate calcium and lead were described as having harder, less ephemoral tissues.

This relationship among calcium, strontium, and lead is consistent with the phenomenon of biopurification described in Section 8.5.2. From the date of Tyler (1982) it appears that some of the species of fungi receive lead from a source other than the nutrient medium, perhaps by direct atmospheric deposition.

8.3.2.2 Effects on Nitrifying Bacteria. The conversion of ammonia to nitrate in soil is a two-step process mediated by two genera of bacteria, Nitrosomonas and Nitrobacter. Nitrate is required by all plants, although some maintain a symbiotic relationship with nitrogen-fixing bacteria as an alternate source of nitrogen. Those which do not would be affected by a loss of free-living nitrifying bacteria, and it is known that many trace metals inhibit this nitrifying process (Liang and Tabatabai, 1977,1978). Lead is the least of these, inhibiting nitrification 14 percent at concentrations of 1,000 µg/g soil. Many metals, even the nutrient metals, manganese and iron, show greater inhibition at comparable molar concentrations. Nevertheless, soils with environmental concentrations above 1,000 µg Pb/g are frequently found. Even a 14 percent inhibition of nitrification can reduce the potential success of a plant population, as nitrate is usually the limiting nutrient in terrestrial ecosystems. In cultivated ecosystems, nitrification inhibition is not a problem if nitrate fertilizer is added to soil, but could reduce the effectiveness of ammonia fertilizer if the crops rely on nitrifying bacteria for conversion to nitrates.

8.3.2.3 Methylation by Aquatic Microorganisms. While methyllead is not a primary form of environmental lead, methylation greatly increases the toxicity of lead to aquatic organisms (Wong and Chau, 1979). There is some uncertainty about whether the mechanism of methylation is biotic or abiotic. Some reports (Wong and Chau, 1979, Thompson and Crerar, 1980) conclude that lead in sediments can be methylated by bacteria. Reisinger et al. (1981) report that biomethylation of lead under aerobic or anaerobic conditions does not occur and such reports are probably due to sulfide-induced chemical conversion of organic lead salts. These authors generally agree that tetramethyl lead can be formed under environmental conditions when another tetravalent organolead compound is available, but methylation of divalent lead salts such as $Pb(NO_3)_2$ does not appear to be significant.

8.3.2.4 Summary of Effects on Microorganisms. It appears that microorganisms are more sensitive than plants to soil lead pollution and that changes in the composition of bacterial

populations may be an early indication of lead effects. Delayed decomposition may occur at 750 µg Pb/g soil and nitrification inhibition at 1,000 µg/g. Many of the environmental variables which can raise or lower these estimates are not yet known. In certain chemical environments, the highly toxic tetramethyllead can be formed, but this process does not appear to be mediated by aquatic microorganisms.

8.4 EFFECTS OF LEAD ON DOMESTIC AND WILD ANIMALS

8.4.1 Vertebrates

8.4.1.1 Terrestrial Vertebrates. Forbes and Sanderson (1978) have reviewed reports of lead toxicity in domestic and wild animals. Lethal toxicity can usually be traced to consumption of lead battery casings, lead-based paints, oil wastes, putty, linoleum, pesticides, lead shot, or forage near smelters. Except for lead shot ingestion, these problems can be solved by proper management of domestic animals. However, the 3,000 tons of lead shot distributed annually along waterways and other hunting grounds continues to be a problem. Of the estimated 80 to 90 million waterfowl in North America, 3.5 million die of poisoning from lead shot annually (U.S. Fish and Wildlife Service, 1976).

A single pellet of lead shot weighs about 110 mg, and 70 percent of this may be eroded in ringed turtle dove gizzards over a period of 14 days (Kendall et al., 1982). Their data showed an immediate elevation of blood lead and reduction of ALA-D activity within 1 day of swallowing two pellets.

Awareness of the routes of uptake is important in interpreting the exposure and accumulation in vertebrates. Inhalation rarely accounts for more than 10 to 15 percent of the daily intake of lead (National Academy of Sciences, 1980). Much of the inhaled lead is trapped on the walls of the bronchial tubes and passes to the stomach embedded in swallowed mucus. Because lead in lakes or running stream water is quite low, intake from drinking water may also be insignificant unless the animal drinks from a stagnant or otherwise contaminated source.

Food is the largest contributor of lead to animals. The type of food an herbivore eats determines the rate of lead ingestion. More than 90 percent of the total lead in leaves and bark may be surface deposition, but relatively little surface deposition may be found on some fruits, berries, and seeds which have short exposure times. Roots intrinsically have no surface deposition. Similarly, ingestion of lead by a carnivore depends mostly on deposition on herbivore fur and somewhat less on lead in herbivore tissue.

The type of food eaten is a major determinant of lead body burdens in small mammals. Goldsmith and Scanlon (1977) and Scanlon (1979) measured higher lead concentrations in insectivorous species than in herbivorous species, confirming the earlier work of Quarles et al.

(1974), which showed body burdens of granivores < herbivores < insectivores, and Jeffries and French (1972) that granivores < herbivores. Animals in these studies were analyzed whole minus the digestive tract. It is likely that observed diet-related differences were somewhat diluted by including fur in the analysis, because fur-lead might be similar for small mammals from the same habitats with different feeding habits.

Since 1977, there has been a trend away from whole body analyses toward analysis of isolated tissues, especially bones and blood. Bone concentrations of lead are better than blood as indicators of long term exposure. Because natural levels of blood lead are not well known for animals and blood is not a good indicator of chronic exposure, blood lead is poorly suited for estimating total body burdens. One experiment with sheep shows the rapid response of blood to changes in lead ingestion and the relative contribution of food and air to the total blood level. Ward et al. (1978) analyzed the blood in sheep grazing near a highway (0.9 µg/g ml) and in an uncontaminated area (0.2 µg/ml). When sheep from the uncontaminated area were allowed to graze near the roadway, their blood levels rose rapidly (within 1 day) to about 3.0 µg/ml, then decreased to 2.0 µg/ml during the next 2 days, remaining constant for the remainder of the 14-day period. Sheep from the contaminated area were moved to the uncontaminated area, where upon their blood dropped to 0.5 µg/ml in 10 days and decreased to 0.3 µg/ml during the next 180 days. Sheep in the uncontaminated area that were fed forage from the roadside experienced an increase in blood lead from 0.2 to 1.1 µg/ml in 9 days. Conversely, sheep from the uncontaminated area moved to the roadside but fed forage only from the uncontaminated site experienced an increase from 0.2 to 0.5 µg/ml in 4 days. These data show that both air and food contribute to lead in blood and that blood lead concentrations are a function of both the recent history of lead exposure and the long term storage of lead in bone tissue.

Chmiel and Harrison (1981) showed that the highest concentrations of lead occurred in the bones of small mammals (Table 8-2), with kidney and liver concentrations somewhat less. They also showed greater bone concentrations in insectivores than herbivores, both at the control and contaminated sites. Clark (1979) found lead concentrations in shrews, voles, and brown bats from roadside habitats near Washington, D.C., to be higher than any previously reported. His estimates of dosages (7.4 mg Pb/kg·day) exceed those that normally cause mortality or reproductive impairment in domestic mammals (1.5-9 mg Pb/g·day) (Hammond and Aronson, 1964; James et al., 1966; Kelliher et al., 1973). Traffic density was the same as reported by Chmiel and Harrison (1981), nearly twice that of Goldsmith and Scanlon (1977) (See Table 8-2). The body lead burden of shrews exceeded mice, which exceeded voles. Beresford et al. (1981) found higher lead in box turtles within 500 m of a lead smelter than in those from control sites. Bone lead exceeded kidney and liver lead as in small mammals.

There are few studies reporting lead in vertebrate tissues from remote sites. Elias et al. (1976, 1982) reported tissue concentrations in voles, shrews, chipmunks, tree squirrels, and pine martens from the remote High Sierra. Bone concentrations were generally only 2 percent of those reported from roadside studies and 10 percent of the controls of roadside studies (Table 8-2), indicating the controls were themselves contaminated to a large degree. Furthermore, biogeochemical calculations suggest that even animals in remote areas have bone lead concentrations 50 to 500 times natural background levels. The natural concentration of lead in the bones of herbivores is about 0.04 ng/g dry weight (Table 8-1). This value may vary regionally with geochemical anomalies in crustal rock, but provides a reasonable indicator of contamination. Natural levels of lead in carnivore bone tissue should be somewhat lower, with omnivores generally in between (Elias and Patterson, 1980; Elias et al., 1982).

Table 8-2 shows the results of several studies of small animal bone tissue. To convert reported values to a common basis, assumptions were made of the average water content, calcium concentration, and average crustal concentration. Because ranges of natural concentrations of lead in bones, plants, soils, and air are known with reasonable certainty (Table 8-1), it is possible to estimate the degree of contamination of vertebrates from a wide range of habitats. It is important to recognize that these are merely estimates that do not allow for possible errors in analysis or anomalies in regional crustal abundances of lead.

8.4.1.2 Effects on Aquatic Vertebrates. Two requirements limit the evaluation of literature reports of lead effects on aquatic organisms. First, any laboratory study should incorporate the entire life cycle of the organism studied. It is clear that certain stages of a life cycle are more vulnerable than others (Hodson, 1979, Hodson et al., 1979). For fish, the egg or fry is usually most sensitive. Secondly, the same index must be used to compare results. Christensen et al. (1977) proposed three indices useful for identifying the effects of lead on organisms. A molecular index reports the maximum concentration of lead causing no significant biochemical change; residue index is the maximum concentration showing no continuing increase of deposition in tissue; and a bioassay index is the maximum concentration causing no mortality, growth change, or physical deformity. These indices are comparable to those of physiological dysfunction (molecular, tissue, and organismic) discussed in Section 8.1.4.

From the standpoint of environmental protection, the most useful index is the molecular index. This index is comparable to the point of initial response discussed previously and is equivalent to the "safe concentration" originally described by the U.S. Environmental Protection Agency (Batelle, 1971) as being the concentration that permits normal reproduction, growth, and all other life-processes of all organisms. It is unfortunate that very few of the toxicity studies in the aquatic literature report safe concentrations as defined above. Nearly all report levels at which some or all of the organisms die.

TABLE 8-2. ESTIMATES OF THE DEGREE OF CONTAMINATION OF HERBIVORES, OMNIVORES, AND CARNIVORES

Data are based on published concentrations of lead in bone tissue (corrected to dry weight as indicated). Degree of contamination is calculated as observed/natural Pb. Natural lead concentrations are from Table 8-1. Concentrations are in µg Pb/g dw.

Organism	Bone Pb conc.	Ref.	Estimated degree of contamination bone
Herbivores			
Vole-roadside	38	1	320
Vole-roadside	17	2	140
-control	5	2	42
Vole-orchard	73	5	610
-control	9	5	75
Vole-remote	2	11	17
Deer mouse-roadside	25	2	210
-control	5.7	2	48
Deer mouse-roadside	29	3	240
-control	7.2	3	60
Deer mouse-roadside	52	4	430
-control	5	4	42
Mouse-roadside	19	2	160
-control	9.3	2	78
Mouse-roadside	109	2	910
-control	18	2	150
Average herbivore			
roadside (7)	41		340
control (7)	8.5		71
remote (2)	2		17
Omnivores/frugivores			
Woodmouse-roadside	67	1	840
-control	25	1	310
Composite-roadside	22	7	280
-control	3	7	37
Chipmunk-remote	2	1	25
Tree squirrel-remote	1.3	11	16
Feral pigeon-urban	670	6	8400
-rural	5.7	6	71
Feral pigeon-urban	250	12	3100
-suburan	33	12	410
-rural	12	12	150
Starling-roadside	210	7	2600
-control	13	7	160

(continued)

TABLE 8-2. (continued)

Organism	Bone Pb conc.	Ref.	Estimated degree of contamination bone
Robin-roadside	130	7	1600
-control	41	7	510
Sparrow-roadside	130	7	1600
-control	17	7	200
Blackbird-roadside	90	7	1100
-control	7	7	88
Grackle-roadside	63	7	790
-control	22	7	280
Rats-roadside	310[a]	9	10000
-control	15[a]	9	500
Average omnivore			
roadside (7)	102		1260
urban (1)	670		8400
control (7)	18		230
remote (2)	1.7		21
Carnivores			
Box turtle-smelter	91[a]	8	3000
-control	5.7[a]	8	190
Egret-rural	12[a]	10	400
Gull-rural	11[a]	10	370
Shrew-roadside	67	2	2200
-control	12	2	400
Shrew-roadside	193	1	6400
-control	41	1	1400
Shrew-remote	4.6	1	150
Pine marten-remote	1.4	11	47
Average carnivore			
roadside (3)	190		6200
smelter (1)	91		3000
rural (2)	11		385
control (4)	18		620
remote (2)	3		99

[a]Dry weight calculated from published fresh weights assuming 35 percent water.

1. Chmiel and Harrison, 1981
2. Getz et al., 1977b
3. Welch and Dick, 1975
4. Mierau and Favara, 1975
5. Elfving et al., 1978
6. Hutton and Goodman, 1980
7. Getz et al., 1977a
8. Beresford et al., 1981
9. Mouw et al., 1975
10. Hulse et al., 1980
11. Elias et al., 1982
12. Johnson et al., 1982b

Hematological and neurological responses are the most commonly reported effects of extended lead exposures in aquatic vertebrates. Hematological effects include the disabling and destruction of mature red blood cells and the inhibition of the enzyme ALA-D required for hemoglobin synthesis. At low exposures, fish compensate by forming additional red blood cells. These red blood cells often do not reach maturity. At higher exposures, the fish become anemic. Symptoms of neurological responses are difficult to detect at low exposure, but higher exposure can induce neuromuscular distortion, anorexia, and muscle tremors. Spinal curvature eventually occurs with time or increased concentration (Hodson 1979; Hodson et al., 1977). Weis and Weis (1982) found spinal curvature in developing eggs of killifish when the embryos had been exposed to 10 µg Pb/ml during the first 7 days after fertilization. All batches showed some measure of curvature, but those that were most resistant to lead were least resistant to the effects of methylmercury.

The biochemical changes used by Christensen et al. (1977) to determine the molecular index for brook trout were 1) increases in plasma sodium and chloride and 2) decreases in glutamic oxalacetic transaminase activity and hemoglobin. They observed effects at 0.5 µg/l, which is 20-fold less than the lower range (10 µg/l) suggested by Wong et al. (1978) to cause significant detrimental effects. Hodson et al. (1978a) found tissue accumulation and blood parameter changes in rainbow trout at 13 µg/l. This was the lowest experimental level, and only slightly above the controls, which averaged 4 µg/l. They concluded, however, that because spinal curvature does not occur until exposures reach 120 µg/l, rainbow trout are adequately protected at 25 µg/l.

Aside from the biochemical responses discussed by Christensen et al. (1977), the lowest reported exposure concentration that causes hematological or neurological effects is 8 µg/l (Hodson, 1979). Christensen's group dealt with subcellular responses, whereas Hodson's group dealt primarily with responses at the cellular or higher level. Hodson et al. (1978a) also reported that lead in food is not available for assimilation by fish, that most of their lead comes from water, and that decreasing the pH of water (as in acid rain) increases the uptake of lead by fish (Hodson et al., 1978b). Patrick and Loutit (1978), however, reported that tissue lead in fish reflects the lead in food if the fish are exposed to the food for more than a few days. Hodson et al. (1980) also reported that, although the symptoms are similar (spinal deformation), lead toxicity and ascorbic acid deficiency are not metabolically related.

8.4.2 Invertebrates

Insects have lead concentrations that correspond to those found in their habitat and diet. Herbivorous invertebrates have lower concentrations than do predatory types (Wade et al.,

1980). Among the herbivorous groups, sucking insects have lower lead concentrations than chewing insects, especially in regions near roadsides, where more lead is found on the surfaces of vegetation. Williamson and Evans (1972) found gradients away from roadsides are not the same as with vertebrates, in that invertebrate lead decreases more slowly than vertebrate lead relative to decreases in soil lead. They also found great differences between major groups of invertebrates. Wood lice in the same habitat, eating the same food, had eight times more lead than millipedes.

The distribution of lead among terrestrial gastropod tissues was reported by Ireland (1979). He found little difference among the foot, skin, mantle, digestive gland, gonad, and intestine. There are no reports of lead toxicity in soil invertebrates. In a feeding experiment, however, Coughtrey et al. (1980) found decreased tolerance for lead by microorganisms from the guts of insects at 800 µg Pb/g food. Many roadside soils fall in this range.

In Cepaea hortensis, a terrestrial snail, Williamson (1979) found most of the lead in the digestive gland and gonadal tissue. He also determined that these snails can lose 93 percent of their whole body lead burden in 20 days when fed a low-lead diet in the laboratory. Since no analyses of the shell were reported, elimination of lead from this tissue cannot be evaluated. A continuation of the study (Williamson, 1980) showed that body weight, age, and day-length influenced the lead concentrations in soft tissues.

Beeby and Eaves (1983) addressed the question of whether uptake of lead in the garden snail, Helix aspersa, is related to the nutrient requirement for calcium during shell formation and reproductive activity. They found both metals were strongly correlated with changes in dry weight and little evidence for correlation of lead with calcium independent of weight gain or loss. Lead in the diet remained constant.

Gish and Christensen (1973) found lead in whole earthworms to be correlated with soil lead, with little rejection of lead by earthworms. Consequently, animals feeding on earthworms from high lead soils might receive toxic amounts of lead in their diets, although there was no evidence of toxic effects on the earthworms (Ireland, 1977). Ash and Lee (1980) cleared the digestive tracts of earthworms and still found direct correlation of lead in earthworms with soil lead; in this case, soil lead was inferred from fecal analyses. These authors found differences among species of earthworms. Ireland and Richards (1977) also found species differences in earthworms, as well as some localization of lead in subcellular organelles of chloragogue and intestinal tissue. In view of the fact that chloragocytes are believed to be involved with waste storage and glycogen synthesis, the authors concluded that this tissue is used to sequester lead in the manner of vertebrate livers. Species differences in whole body lead concentrations could not be attributed to selective feeding or differential absorption, unless the differential absorption occurs only at elevated lead concentrations.

The authors suggested that the two species have different maximum tolerances for body lead but gave no indication of physiological dysfunction when the maximum tolerance was reached. In soils with a total lead concentration of 1,800 µg/g dry weight (Ireland, 1975), Lumbricus rubellus had a whole body concentration of 3,600 µg/g, while Dendrobaene rubida accumulated 7,600 µg/g in the same location (Ireland and Richards, 1977). Because this difference was not observed at the control site (15 µg/g soil), it can be assumed that at some soil concentration between 15 and 1,800 µg/g, different species of earthworms begin to accumulate different amounts of lead. The authors concluded that D. rubida can simply tolerate higher tissue lead concentrations, implying that soil concentrations of 1,800 µg/g are toxic to L. rubellus. This concentration would be considerably lower than soil lead concentrations that cause effects in plants, and similar to that which can affect soil microorganisms.

Aquatic insects appear to be resistant to high levels of lead in water. To be conclusive, toxicity studies must observe invertebrates through an entire life cycle, although this is infrequently done. Anderson et al. (1980) found LC_{50}'s for eggs and larvae of Tanytarsus dissimilis, a chironomid, to be 260 µg/l. This value is 13 to 250 times lower than previously reported by Warnick and Bell (1969), Rehwoldt et al. (1973), and Nehring (1976). However, Spehar et al. (1978) found that mature amphipods (Gammarus pseudolimnaeus) responded negatively to lead at 32 µg/l. Fraser et al. (1978) found that adult populations of a freshwater isopod (Asellus aquaticus) have apparently developed a genetic tolerance for lead in river sediments.

Newman and McIntosh (1982) investigated freshwater gastropods, both grazing and burrowing. Lead concentrations in the grazers (Physa integra, Pseudosuccinea columella, and Helisoma trivolvis) were more closely correlated with water concentrations than with lead in the food. Lead in the burrowing species, Campeloma decisum, was not correlated with any environmental factor. These authors (Newman and McIntosh, 1983) also reported that both Physa integra and Campeloma decisum are able to eliminate lead from their soft tissue when transferred to a low-lead medium, but that tissue lead stabilized at a level higher than found in populations living permanently in the low-lead environment. This would seem to indicate the presence of a persistent reservoir of lead in the soft tissues of these gastropods.

Borgmann et al. (1978) found increased mortality in a freshwater snail, Lymnaea palutris, associated with stream water with a lead content as low as 19 µg/l. Full life cycles were studied to estimate population productivity. Although individual growth rates were not affected, increased mortality, especially at the egg hatching stage, effectively reduced total biomass production at the population level. Production was 50 percent at 36 µg/l and 0 percent at 48 µg Pb/l.

The relationship between LC_{50} and initial physiological response is not immediately obvious. It is certain that some individuals of a population experience physiological dysfunction well before half of them die. For example, Biesinger and Christensen (1972) observed minimum reproductive impairment in Daphnia at 6 percent of the LC_{50} (450 µg/l) for this species.

8.4.3 Summary of Effects on Animals

While it is impossible to establish a safe limit of daily lead consumption, it is reasonable to generalize that a regular diet of 2 to 8 mg Pb/kg·day body weight over an extended period of time (Botts, 1977) will cause death in most animals. Animals of the grazing food chain are affected most directly by the accumulation of aerosol particles on vegetation surfaces and somewhat indirectly by the uptake of lead through plant roots. Many of these animals consume more than 1 mg Pb/kg·day in habitats near smelters and roadsides, but no toxic effects have been documented. Animals of the decomposer food chain are affected indirectly by lead in soil which can eliminate populations of microorganisms preceeding animals in the food chain or occupying the digestive tract of animals and aiding in the breakdown of organic matter. Invertebrates may also accumultate lead at levels toxic to their predators.

Aquatic animals are affected by lead at water concentrations lower than previously considered safe (50 µg Pb/l) for wildlife. These concentrations occur commonly, but the contribution of atmospheric lead to specific sites of high aquatic lead is not clear.

8.5 EFFECTS OF LEAD ON ECOSYSTEMS

There is wide variation in the mass transfer of lead from the atmosphere to terrestrial ecosystems. Even within the somewhat artificial classification of undisturbed, cultivated, and urban ecosystems, reported fluxes in undisturbed ecosystems vary by nearly 20-fold. Smith and Siccama (1981) report 270 g/ha·yr in the Hubbard Brook forest of New Hampshire; Lindberg and Harriss (1981) found 50 g/ha·yr in the Walker Branch watershed of Tennessee; and Elias et al. (1976) found 15 g/ha·yr in a remote subalpine ecosystem of California. Jackson and Watson (1977) found 1,000,000 g/ha·yr near a smelter in southeastern Missouri. Getz et al. (1979) estimated 240 g/ha·yr by wet precipitation alone in a rural ecosystem largely cultivated and 770 g/ha·yr in an urban ecosystem.

One factor causing great variation is remoteness from source, which translates to lower air concentrations, smaller particles, and greater dependence on wind as a mechanism of deposition (Elias and Davidson, 1980). Another factor is type of vegetation cover. Deciduous leaves may, by the nature of their surface and orientation in the wind stream, be more suitable deposition surfaces than conifer needles. Davidson et al. (1982) discussed the influence of leaf surface on deposition rates to grasses.

The history of lead contamination in roadside ecosystems has been reviewed by Smith (1976). Recent studies have shown three areas of concern where the effects of lead on ecosystems may be extremely sensitive (Martin and Coughtrey, 1981; Smith, 1981). First, decomposition is delayed by lead, as some decomposer microorganisms and invertebrates are inhibited by soil lead. Secondly, the natural processes of calcium biopurification are circumvented by the accumulation of lead on the surfaces of vegetation and in the soil reservoir. Thirdly, some ecosystems experience subtle shifts toward lead tolerant plant populations. These problems all arise because lead in ecosystems is deposited on vegetation surfaces, accumulates in the soil reservoir, and is not removed with the surface and ground water passing out of the ecosystem. Other potential effects are discussed that may occur because of the longterm build-up of lead in soil.

8.5.1 Delayed Decomposition

The flow of energy through an ecosystem is regulated largely by the ability of organisms to trap energy in the form of sunlight and to convert this energy from one chemical form to another (photosynthesis). Through photosynthesis, plants convert light to stored chemical energy. Starch is only a minor product of this energy conversion. The most abundant substance produced by net primary production is cellulose, a structural carbohydrate of plants. Terrestrial ecosystems, especially forests, accumulate a tremendous amount of cellulose as woody tissue of trees. Few animals can digest cellulose and most of these require symbiotic associations with specialized bacteria. It is no surprise then, that most of this cellulose must eventually pass through the decomposer food chain. Litter fall is the major route for this pathway. Because 80 percent or more of net primary production passes through the decomposing food chain (Swift et al., 1979), the energy of this litter is vital to the rest of the plant community and the inorganic nutrients are vital to plants.

The amount of lead that causes litter to be resistant to decomposition is not known. Although laboratory studies show that 50 µg Pb/ml nutrient medium definitely inhibits soil bacterial populations, field studies indicate little or no effect at 600 µg/g litter (Doelman and Haanstra, 1979b). One explanation is that the lead in the laboratory nutrient medium was readily available, while the lead in the litter was chemically bound to soil organic matter. Indeed, Doelman and Haanstra (1979a) demonstrated the effects of soil lead content on delayed decomposition: sandy soils lacking organic complexing compounds showed a 30 percent inhibition of decomposition at 750 µg/g, including the complete loss of major bacterial species, whereas the effect was reduced in clay soils and non-existent in peat soils. Organic matter maintains the cation exchange capacity of soils. A reduction in decomposition rate was observed by Doelman and Haanstra (1979a) even at the lowest experimental concentration of lead, leading to the conclusion that some effect might have occurred at even lower concentrations.

When decomposition is delayed, nutrients may be limiting to plants. In tropical regions or areas with sandy soils, rapid turnover of nutrients is essential for the success of the forest community. Even in a mixed deciduous forest, a significant portion of the nutrients, especially nitrogen and sulfur, may be found in the litter reservoir (Likens et al. 1977). Annual litter inputs of calcium and nitrogen to the soil account for about 60 percent of root uptake. With delayed decomposition, plants must rely on precipitation and soil weathering for the bulk of their nutrients. Furthermore, the organic content of soil may decrease, reducing the cation exchange capacity of soil.

8.5.2 Circumvention of Calcium Biopurification

Biopurification is a process that regulates the relative concentrations of nutrient to non-nutrient elements in biological components of a food chain. In the absence of absolute knowledge of natural lead concentrations, biopurification can be a convenient method for estimating the degree of contamination. Following the suggestion by Comar (1966) that carnivorous animals show reduced Sr/Ca ratios compared to herbivorous animals which, in turn show less than plants, Elias et al. (1976, 1982) developed a theory of biopurification, which hypothesizes that calcium reservoirs are progressively purified of Sr, Ba, and Pb in successive stages of a food chain. In other words, if the Sr/Ca and Ba/Ca ratios are known, the natural Pb/Ca ratio can be predicted and the observed Pb/Ca to natural Pb/Ca ratio is an expression of the degree of contamination. Elias et al. (1976, 1982) and Elias and Patterson (1980) observed continuous biopurification of calcium in grazing and detrital food chains by the progressive exclusion of Sr, Ba, and Pb (Figure 8-5). It is now believed that members of grazing and decomposer food chains are contaminated by factors of 30 to 500, i.e., that 97 percent to 99.9 percent of the lead in organisms is of anthropogenic origin. Burnett and Patterson (1980) have shown a similar pattern for a marine food chain.

The mechanism of biopurification relies heavily on the selective transport of calcium across membranes, the selective retention of non-nutrients at physiologically inactive binding sites, and the reduced solubility of non-nutrient elements in the nutrient medium of plants and animals. For example, lead is bound more vigorously to soil organic complexes and is less soluble in soil moisture (Section 6.5.1). Lead is also adsorbed to cell walls in the root apoplast, is excluded by the cortical cell membrane, and is isolated as a precipitate in subcellular vesicles of cortical cells (Koeppe, 1981). Further selectivity at the endodermis results in a nutrient solution of calcium in the vascular tissue which is greatly purified of lead. Similar mechanisms occur in the stems and leaves of plants, in the digestive and circulatory systems of herbivores and carnivores, and in the nutrient processing mechanisms of insects.

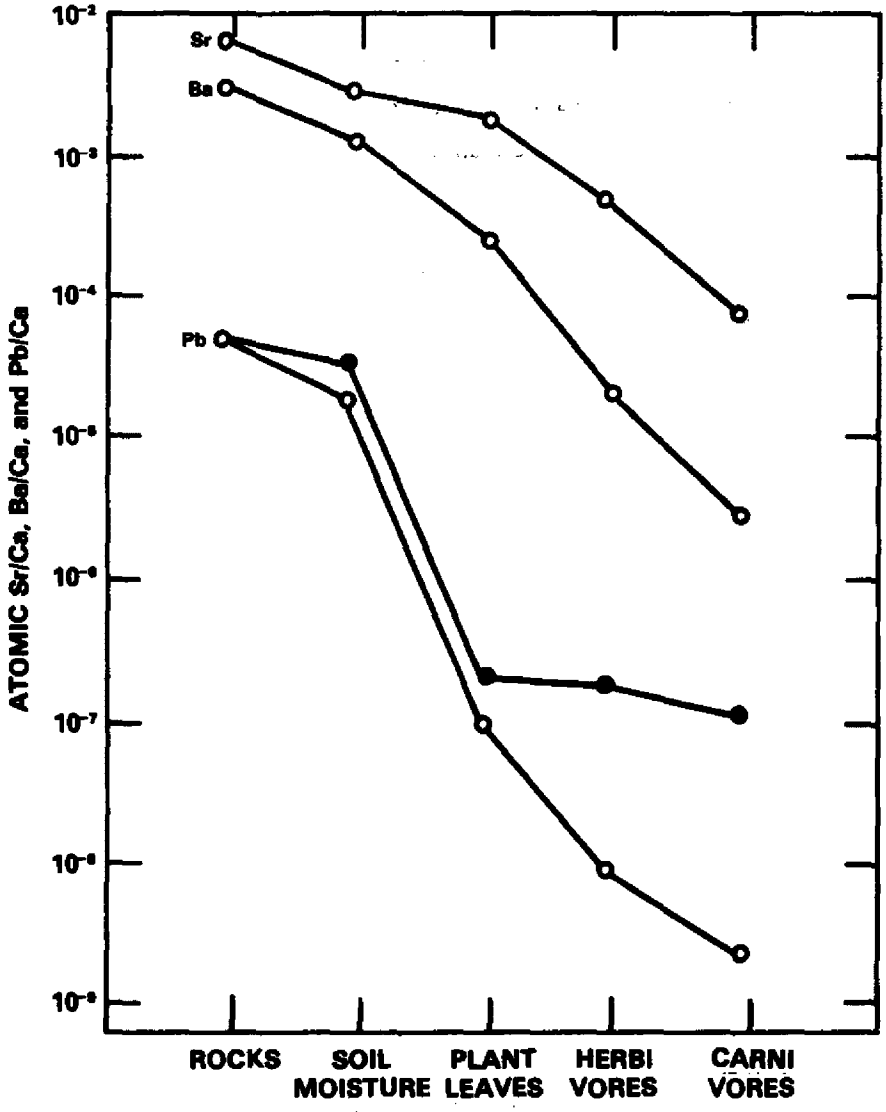

Figure 8-5. The atomic ratios Sr/Ca, Ba/Ca and Pb/Ca (O) normally decrease by several orders of magnitude from the crustal rock to ultimate carnivores in grazer and decomposer food chains. Anthropogenic lead in soil moisture and on the surfaces of vegetation and animal fur interrupt this process to cause elevated Pb/Ca ratios (●) at each stage of the sequence. The degree of contamination is the ratio of Total Pb/Ca *vs.* Natural Pb/Ca at any stage. Ba/Ca and Sr/Ca ratios are approximate guidelines to the expected natural Pb/Ca ratio.

Source: Adapted from Elias et al. (1982).

Atmospheric lead circumvents the natural biopurification of calcium. Deposition on plant surfaces, which accounts for 90 percent of the total plant lead, increases the ratio of Pb/Ca in the diet of herbivores. Deposition on animal fur increases the Pb/Ca ratio in the diet of carnivores. Atmospheric lead consumed by inhalation or grooming, possibly 15 percent of the total intake of lead, represents sources of lead which were non-existent in prehistoric times and therefore were not present in the food chain.

8.5.3 Population Shifts Toward Lead Tolerant Populations

It has been observed that plant communities near smelter sites are composed mostly of lead tolerant plant populations (Antonovics et al., 1971). In some cases, these populations appear to have adapted to high-lead soils, since populations of the same species from low-lead soils often do not thrive on high-lead soils (Jowett, 1964). Similar effects have been observed for soils enriched to 28,000 µg/g dry weight with ore lead (Høiland and Oftedal, 1980) and near roadsides at soil concentrations of 1,300 µg/g dry weight (Atkins et al., 1982). In these situations, it is clear that soil lead concentration has become the dominant factor in determining the success of plant populations and the stability of the ecological community. Soil moisture, soil pH, light intensity, photoperiod, and temperature are all secondary factors (Antonovics et al., 1971). Strategies for efficient use of light and water, and for protection from temperature extremes, are obliterated by the succession of lead-tolerant plant populations. Smith and Bradshaw (1972) concluded that lead-tolerant plant populations of Festuca rubra and Agrostis tenuis can be used to stabilize toxic mine wastes with lead concentrations as high as 80,000 µg/g.

8.5.4 Mass Balance Distribution of Lead in Ecosystems

Inputs of natural lead to ecosystems, approximately 90 percent from rock weathering and 10 percent from atmospheric sources, account for slightly more than the hydrologic lead outputs in most watersheds (Patterson, 1980). The difference is small and accumulation in the ecosystem is significant only over a period of several thousand years. In modern ecosystems, with atmospheric inputs exceeding weathering by factors of 10 to 1000, greater accumulation occurs in soils and this reservoir must be treated as lacking a steady state condition (Heinrichs and Mayer, 1977, 1980; Siccama and Smith, 1978). Odum and Drifmeyer (1978) describe the role of detrital particles in retaining a wide variety of pollutant substances, and this role may be extended to include non-nutrient substances.

It appears that plant communities have a built-in mechanism for purifying their own nutrient medium. As a plant community matures through successional stages, the soil profile develops a stratified arrangement which retains a layer of organic material near the surface.

This organic layer becomes a natural site for the accumulation of lead and other non-nutrient metals which might otherwise interfere with the uptake and utilization of nutrient metals. But the rate accumulation of lead in this reservoir may eventually exceed the capacity of the reservoir. Johnson et al. (1982a) have established a baseline of 80 stations in forests of the northeast United States. In the litter component of the forest floor, they measured an average lead concentration of 150 μg/g. Near a smelter, they measured 700 μg/g and near a highway, 440 μg/g. They presented some evidence from buried litter that predevelopment concentrations were 24 μg/g. On an area basis, the present concentrations range from 0.7 to 1.8 g Pb/m^2. Inputs of 270 g/ha·yr measured in the Hubbard Brook forest (see Section 8.5) would account for 1.0 g Pb/m^2 in forty years if all of the lead were retained. The 80 stations will be monitored regularly to show temporal changes. Evidence for recent changes in litter lead concentrations is documented in the linear relationship between forest floor lead concentration and age of forest floor, up to 100 years.

Lead in the detrital reservoir is determined by the continued input of atmospheric lead from the litter layer, the passage of detritus through the decomposer food chain, and the rate of leaching into soil moisture. There is strong evidence that soil has a finite capacity to retain lead (Zimdahl and Skogerboe, 1977). Harrison et al. (1981) observed that most of the lead in roadside soils above 200 μg/g is found on Fe-Mn oxide films or as soluble lead carbonate. Elias et al. (1982) have shown that soil moisture lead is derived from the leachable/organic fraction of soil, not the inorganic fraction. Lead is removed from the detrital reservoir by the digestion of organic particles in the detrital food chain and by the release of lead to soil moisture. Both mechanisms result in a redistribution of lead among all of the reservoirs of the ecosystem at a very slow rate. A closer look at the mechanisms whereby lead is bound to humic and fulvic acids leads to the following conclusions: 1) because lead has a higher binding strength than other metals, lead can displace other metals on the organic molecule (Schnitzer and Khan, 1978); 2) if calcium is displaced, it would be leached to a lower soil horizon (B), where it may accumulate as it normally does during the development of the soil profile; and 3) if other nutrient metals, such as iron or manganese, are displaced, they may become unavailable to roots as they pass out of the soil system.

Fulvic acid plays an important role in the development of the soil profile. This organic acid has the ability to remove iron from the lattice structures of inorganic minerals, resulting in the decomposition of these minerals as a part of the weathering process. This breakdown releases nutrients for uptake by plant roots. If all binding sites on fulvic acid are occupied by lead, the role of fulvic acid in providing nutrients to plants will be circumvented. While it is reasonably certain that such a process is possible, there is no information about the soil lead concentrations that would cause such an effect.

Ecosystem inputs of lead by the atmospheric route have established new pathways and widened old ones. Insignificant amounts of lead are removed by surface runoff or ground water seepage. It is likely that the ultimate fate of atmospheric lead will be a gradual elevation in lead concentration of all reservoirs in the system, with most of the lead accumulating in the detrital reservoir.

8.6 SUMMARY

Because there is no protection from industrial lead once it enters the atmosphere, it is important to fully understand the effects of industrial lead emissions. Of the 450,000 tons emitted annually on a global basis, 115,000 tons of lead fall on terrestrial ecosystems. Evenly distributed, this would amount to 0.1 g/ha·yr, which is much lower than the range of 15 to 1,000,000 g/ha·yr reported in ecosystem studies in the United States. Lead has permeated these ecosystems and accumulated in the soil reservoir where it will remain for decades (Chapter 6). Within 20 meters of every major highway, up to 10,000 μg Pb have been added to each gram of surface soil since 1930 (Getz et al., 1979). Near smelters, mines, and in urban areas, as much as 130,000 μg/g have been observed in the upper 2.5 cm of soil (Jennett et al., 1977). At increasing distances up to 5 kilometers away from sources, the gradient of lead added since 1930 drops to less than 10 μg/g (Page and Ganje, 1970), and 1 to 5 μg/g have been added in regions more distant than 5 kilometers (Nriagu, 1978). In undisturbed ecosystems, atmospheric lead is retained by soil organic matter in the upper layer of soil surface. In cultivated soils, this lead is mixed with soil to a depth of 25 cm.

Because of the special nature of the soil reservoir, it must not be regarded as an infinite sink for lead. On the contrary, atmospheric lead which is already bound to soil will continue to pass into the grazing and detrital food chains until equilibrium is reached, whereupon the lead in all reservoirs will be elevated proportionately higher than natural background levels. This conclusion applies also to cultivated soils, where lead bound within the upper 25 cm is still within the root zone.

Few plants can survive at soil concentrations in excess of 20,000 μg/g, even under optimum conditions. Some key populations of soil microorganisms and invertebrates die off at 1000 μg/g. Herbivores, in addition to a normal diet from plant tissues, receive lead from the surfaces of vegetation in amounts that may be 10 times greater than from internal plant tissue. A diet of 2 to 8 mg/day·kg body weight seems to initiate physiological dysfunction in many vertebrates.

Whereas previous reports have focused on possible toxic effects of lead on plants, animals, and humans, it is essential to consider the degree of contamination as one measure of safe concentration. Observed toxic effects occur at environmental concentrations well above

levels that cause no physiological dysfunction. Small animals in undisturbed ecosystems are contaminated by factors of 20 to 600 over natural background levels, and in roadside and urban ecosystems by 300 to 6200. Extrapolations based on sublethal effects may become reliable when these measurements can be made with controls free of contamination. The greatest impact may be on carnivorous animals, which generally have the lowest concentrations of natural lead, and may thus havet he greatest percent increase when the final equilibrium is reached.

Perhaps the most subtle effect of lead is on ecosystems. The normal flow of energy through the decomposer food chain may be interrupted, the composition of communities may shift toward more lead-tolerant populations, and new biogeochemical pathways may be opened, as lead flows into and throughout the ecosystem. The ability of an ecosystem to compensate for atmospheric lead inputs, especially in the presence of other pollutants such as acid precipitation, depends not so much on factors of ecosystem recovery, but on undiscovered factors of ecosystem stability. Recovery implies that inputs of the perturbing pollutant have ceased and that the pollutant is being removed from the ecosystem. In the case of lead, the pollutant is not being eliminated from the system nor are the inputs ceasing. Terrestrial ecosystems will never return to their original, pristine levels of lead concentrations.

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Volume III of IV

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ABSTRACT

The document evaluates and assesses scientific information on the health and welfare effects associated with exposure to various concentrations of lead in ambient air. The literature through 1983 has been reviewed thoroughly for information relevant to air quality criteria, although the document is not intended as a complete and detailed review of all literature pertaining to lead. An attempt has been made to identify the major discrepancies in our current knowledge and understanding of the effects of these pollutants.

Although this document is principally concerned with the health and welfare effects of lead, other scientific data are presented and evaluated in order to provide a better understanding of this pollutant in the environment. To this end, the document includes chapters that discuss the chemistry and physics of the pollutant; analytical techniques; sources, and types of emissions; environmental concentrations and exposure levels; atmospheric chemistry and dispersion modeling; effects on vegetation; and respiratory, physiological, toxicological, clinical, and epidemiological aspects of human exposure.

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LIST OF ABBREVIATIONS

AAS	Atomic absorption spectrometry
Ach	Acetylcholine
ACTH	Adrenocoticotrophic hormone
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADP/O ratio	Adenosine diphosphate/oxygen ratio
AIDS	Acquired immune deficiency syndrome
AIHA	American Industrial Hygiene Association
AII	Angiotensin II
ALA	Aminolevulinic acid
ALA-D	Aminolevulinic acid dehydrase
ALA-S	Aminolevulinic acid synthetase
ALA-U	Aminolevulinic acid in urine
APDC	Ammonium pyrrolidine-dithiocarbamate
APHA	American Public Health Association
ASTM	Amercian Society for Testing and Materials
ASV	Anodic stripping voltammetry
ATP	Adenosine triphosphate
B-cells	Bone marrow-derived lymphocytes
Ba	Barium
BAL	British anti-Lewisite (AKA dimercaprol)
BAP	benzo(a)pyrene
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
BW	Body weight
C.V.	Coefficient of variation
CaBP	Calcium binding protein
CaEDTA	Calcium ethylenediaminetetraacetate
CBD	Central business district
Cd	Cadmium
CDC	Centers for Disease Control
CEC	Cation exchange capacity
CEH	Center for Environmental Health
CFR	reference method
CMP	Cytidine monophosphate
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CP-U	Urinary coproporphyrin
C_{cpah}	plasma clearance of p-aminohippuric acid
Cu	Copper
D.F.	Degrees of freedom
DA	Dopamine
DCMU	[3-(3,4-dichlorophenyl)-1,1-dimethylurea
DDP	Differential pulse polarography
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
EEC	European Economic Community
EEG	Electroencephalogram
EMC	Encephalomyocarditis
EP	Erythrocyte protoporphyrin
EPA	U.S. Environmental Protection Agency

LIST OF ABBREVIATIONS (continued).

FA	Fulvic acid
FDA	Food and Drug Administration
Fe	Iron
FEP	Free erythrocyte protoporphyrin
FY	Fiscal year
G.M.	Grand mean
G-6-PD	Glucose-6-phosphate dehydrogenase
GABA	Gamma-aminobutyric acid
GALT	Gut-associated lymphoid tissue
GC	Gas chromatography
GFR	Glomerular filtration rate
HA	Humic acid
Hg	Mercury
hi-vol	High-volume air sampler
HPLC	High-performance liquid chromatography
i.m.	Intramuscular (method of injection)
i.p.	Intraperitoneally (method of injection)
i.v.	Intravenously (method of injection)
IAA	Indol-3-ylacetic acid
IARC	International Agency for Research on Cancer
ICD	International classification of diseases
ICP	Inductively coupled plasma
IDMS	Isotope dilution mass spectrometry
IF	Interferon
ILE	Isotopic Lead Experiment (Italy)
IRPC	International Radiological Protection Commission
K	Potassium
LAI	Leaf area index
LDH-X	Lactate dehydrogenase isoenzyme x
LC_{50}	Lethyl concentration (50 percent)
LD_{50}	Lethal dose (50 percent)
LH^{50}	Luteinizing hormone
LIPO	Laboratory Improvement Program Office
ln	National logarithm
LPS	Lipopolysaccharide
LRT	Long range transport
mRNA	Messenger ribonucleic acid
ME	Mercaptoethanol
MEPP	Miniature end-plate potential
MES	Maximal electroshock seizure
MeV	Mega-electron volts
MLC	Mixed lymphocyte culture
MMD	Mass median diameter
MMED	Mass median equivalent diameter
Mn	Manganese
MND	Motor neuron disease
MSV	Moloney sarcoma virus
MTD	Maximum tolerated dose
n	Number of subjects
N/A	Not Available

LIST OF ABBREVIATIONS

NA	Not Applicable
NAAQS	National ambient air quality standards
NADB	National Aerometric Data Bank
NAMS	National Air Monitoring Station
NAS	National Academy of Sciences
NASN	National Air Surveillance Network
NBS	National Bureau of Standards
NE	Norepinephrine
NFAN	National Filter Analysis Network
NFR-82	Nutrition Foundation Report of 1982
NHANES II	National Health Assessment and Nutritional Evaluation Survey II
Ni	Nickel
OSHA	Occupational Safety and Health Administration
P	Potassium
p	Significance symbol
PAH	Para-aminohippuric acid
Pb	Lead
PBA	Air lead
$Pb(Ac)_2$	Lead acetate
PbB	concentration of lead in blood
PbBrCl	Lead (II) bromochloride
PBG	Porphobilinogen
PFC	Plaque-forming cells
pH	Measure of acidity
PHA	Phytohemagglutinin
PHZ	Polyacrylamide-hydrous-zirconia
PIXE	Proton-induced X-ray emissions
PMN	Polymorphonuclear leukocytes
PND	Post-natal day
PNS	Peripheral nervous system
ppm	Parts per million
PRA	Plasma renin activity
PRS	Plasma renin substrate
PWM	Pokeweed mitogen
Py-5-N	Pyrimide-5'-nucleotidase
RBC	Red blood cell; erythrocyte
RBF	Renal blood flow
RCR	Respiratory control ratios/rates
redox	Oxidation-reduction potential
RES	Reticuloendothelial system
RLV	Rauscher leukemia virus
RNA	Ribonucleic acid
S-HT	Serotonin
SA-7	Simian adenovirus
scm	Standard cubic meter
S.D.	Standard deviation
SDS	Sodium dodecyl sulfate
S.E.M.	Standard error of the mean
SES	Socioeconomic status
SGOT	Serum glutamic oxaloacetic transaminase

LIST OF ABBREVIATIONS (continued).

sIg	Surface immunoglobulin
SLAMS	State and local air monitoring stations
SMR	Standardized mortality ratio
Sr	Strontium
SRBC	Sheep red blood cells
SRMs	Standard reference materials
STEL	Short-term exposure limit
SW voltage	Slow-wave voltage
T-cells	Thymus-derived lymphocytes
t-tests	Tests of significance
TBL	Tri-n-butyl lead
TEA	Tetraethyl-ammonium
TEL	Tetraethyllead
TIBC	Total iron binding capacity
TML	Tetramethyllead
TMLC	Tetramethyllead chloride
TSH	Thyroid-stimulating hormone
TSP	Total suspended particulate
U.K.	United Kingdom
UMP	Uridine monophosphate
USPHS	U.S. Public Health Service
VA	Veterans Administration
V_d	Deposition velocity
VER	Visual evoked response
WHO	World Health Organization
XRF	X-Ray fluorescence
X^2	Chi squared
Zn	Zinc
ZPP	Erythrocyte zinc protoporphyrin

MEASUREMENT ABBREVIATIONS

dl	deciliter
ft	feet
g	gram
g/gal	gram/gallon
g/ha·mo	gram/hectare·month
km/hr	kilometer/hour
l/min	liter/minute
mg/km	milligram/kilometer
$\mu g/m^3$	microgram/cubic meter
mm	millimeter
µmol	micrometer
ng/cm^2	nanograms/square centimeter
nm	namometer
nM	nanomole
sec	second

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9. QUANTITATIVE EVALUATION OF LEAD AND BIOCHEMICAL INDICES OF LEAD EXPOSURE IN PHYSIOLOGICAL MEDIA

9.1 INTRODUCTION

In order to completely understand a given agent's effects on an organism, e.g., dose-effect relationships, a quantitative evaluation of the substance in some indicator medium and knowledge of the physiological parameters associated with exposure is vital. This said, two questions follow:

1) What are the most accurate, precise, and efficient ways to carry out such measurements?

2) In the case of lead (lead itself or biological indicators), which measurement methods in which media are most appropriate for each particular exposure?

Under the rubric of "analysis" are a number of discrete steps, all of which are important contributors to the quality of the final result: (1) collection of samples and transmission to the laboratory; (2) laboratory manipulation of samples, physically and chemically, before analysis by instruments; (3) instrumental analysis and quantitative measurement; and (4) establishment of relevant criteria for accuracy and precision, namely, internal and external quality assurance checks. Each of these steps is discussed in this chapter.

It is clear that the definition of "satisfactory analytical method" for lead has been changing over the years in ways paralleling (1) the evolution of more sophisticated instrumentation and procedures, (2) a greater awareness of such factors as background contamination and loss of element from samples, and (3) development of new statistical methods to analyze data. For example, current methods of lead analysis, such as anodic stripping voltammetry, background-corrected atomic absorption spectrometry, and isotope dilution mass spectrometry (particularly the latter), are more sensitive and specific than the older classical approaches. Increasing use of the newer methods would tend to result in lower lead values being reported for a given sample. Whether this trend in analytical improvement can be isolated from such other variables as temporal changes in exposure is another matter.

Since lead is ubiquitously distributed as a contaminant, the constraints (i.e., ultra-clean, ultra-trace analysis) placed upon a laboratory attempting analysis of geochemical samples of pristine origin, or of extremely low lead levels in biological samples such as plasma, are quite severe. Very few laboratories can credibly claim such capability. Ideally, similar standards of quality should be adhered to across the rest of the analytical spectrum. With many clinical, epidemiological, and experimental studies, however, this may be unrealistic, given practical limitations and objectives of the studies. Laboratory performance is but

one part of the quality equation; the problems of sampling are equally important but less subject to tight control. The necessity of rapidly obtaining a blood sample in cases of suspected lead poisoning, or of collecting hundreds or thousands of blood samples in urban populations, limits the number of sampling safeguards to those that can be realistically achieved. Sampling in this context will always be accompanied by a certain amount of analytical "suspicion." Furthermore, a certain amount of biological lead analysis data is employed for comparative purposes, as in experimental studies concerned with the relative increase in tissue burden of lead associated with increases in doses or severity of effects. In addition, any major compromise of an analytical protocol may be statistically discernible. Thus, analysis of biological media for lead must be done under protocols that minimize the risk of inaccuracy. Specific accuracy and precision characteristics of a method in a particular report should be noted to permit some judgment on the part of the reader about the influence of methodology on the reported results.

The choice of measurement method (see Question 2) and medium for analysis is dictated both by the type of information desired and by technical or logistical considerations. As noted elsewhere in this document, whole blood lead reflects recent or continuing exposure, whereas lead in mineralized tissue, such as deciduous teeth, reflects an exposure period of months and years. While urine lead values are not particularly good correlates of lead exposure under steady-state conditions in populations at large, such measurements may be of considerable clinical value. In acquisition of blood samples, the choice of venipuncture or finger puncture will be governed by such factors as cost and feasibility, contamination risk, the biological quality of the sample, etc. The use of biological indicators that strongly correlate with lead burden may be more desirable since they provide evidence of actual response and, together with blood lead data, provide a less risky diagnostic tool for assessment of lead exposure.

9.2 DETERMINATIONS OF LEAD IN BIOLOGICAL MEDIA

9.2.1 Sampling and Sample Handling Procedures for Lead in Biological Media

Lead analysis in biological media requires careful collection and handling of samples for two special reasons: (1) lead occurs at trace levels in most indicators of subject exposure, even under conditions of high lead exposure, and (2) such samples must be obtained against a backdrop of pervasive contamination, the full extent of which may still be unrecognized by many laboratories.

The reports of Speecke et al. (1976), Patterson and Settle (1976), Murphy (1976), Berman (1976), and Settle and Patterson (1980) review detailed aspects of the problems of sampling and subsequent sample handling in the laboratory. It is clear from these discussions that the

normal precautions taken in the course of sample acquisition (detailed below for clinical and epidemiological studies) should not be taken as absolute, but rather as what is practical and feasible. Furthermore, it may also be the case that the inherent sensitivity or accuracy of a given methodology or instrumentation is less of a determining factor in the overall analysis than is quality of sample collection and handling.

9.2.1.1 Blood Sampling. Samples for blood lead determination may be collected by venipuncture (venous blood) or finger tip puncture (capillary blood). Collection of capillary vs. venous blood is normally decided by a number of factors, including the feasibility of obtaining samples during screening of many subjects and the difficulty of securing subject compliance, particularly in the case of children and their parents. Furthermore, capillary blood may be collected as discrete quantities in small-volume capillary tubes or as spots on filter paper disks. With capillary tubes, obtaining good mixing with anticoagulant to avoid clotting is important, as is the problem of lead contamination of the tube. The use of filter paper requires the selection of paper with uniform composition, low lead content, and uniform blood dispersal characteristics.

Whether venous or capillary blood is collected, much care must be exercised in cleaning the site before puncture as well as in selecting lead-free receiving containers. Cooke et al. (1974) employed vigorous scrubbing with a low-lead soap solution and deionized water rinsing, while Marcus et al. (1975) carried out preliminary cleaning with an ethanolic citric acid solution followed by 70 percent ethanol rinsing. The vigor in cleaning the puncture site is probably as important as any particular choice of cleaning agent. Marcus et al. (1977) noted that in one procedure for puncture site preparation, where the site is covered with wet paper towels, contamination will occur if the paper towels are made from recycled paper, owing to significant lead retention in recycled paper.

In theory, capillary and venous blood lead levels should be virtually identical, although the available literature indicates that some differences, which mainly reflect problems of sampling, do arise in the case of capillary blood. A given amount of contaminant has a greater impact on a 100 µl fingerstick sample than on a 5 ml sample of venous blood. Finger coating techniques may reduce some of the contamination problem (Mitchell et al., 1974). An additional problem is the presence of lead in the anticoagulants used to coat capillary tubes. Also, lower values of capillary vs. venous blood lead may reflect "dilution" of the sample by extracellular fluid owing to excessive compression of the puncture site. When Joselow and Bogden (1972) compared a method using finger puncture and spotting onto filter paper with a procedure using venous blood and Hessel's procedure (1968) for flame atomic absorption spectrometry, they obtained a correlation coefficient of $r = 0.9$ (range, 20-46 µg/dl). Similarly, Cooke et al. (1974) found an r value of 0.8 (no range given), while Mitchell et al. (1974)

obtained a value of 0.92 (10-92 µg/dl). Mahaffey et al. (1979) found that capillary blood levels in a comparison test were approximately 20 percent higher than corresponding venous blood levels in the same subjects, presumably reflecting sample contamination. Similar elevations have been described by DeSilva and Donnan (1980). Carter (1978) has found that blood samples with lower hemoglobin levels may spread onto filter paper differently from normal hemoglobin samples, requiring correction in quantification to obtain values that are reliable. This complication should be kept in mind when considering children, who are frequently prone to iron-deficiency anemia.

The relative freedom of the blood container from interior surface lead and the amount of lead in the anticoagulant used are important considerations in venous sampling. For studies focused on "normal" ranges, such tubes may add some lead to blood and still meet certification requirements. The "low-lead" heparinized blood tubes commercially available (blue stopper Vacutainer, Becton-Dickinson) were found to contribute less than 0.2 µg/dl to whole blood samples (Rabinowitz and Needleman, 1982). Nackowski et al. (1977) surveyed a large variety of commercially available blood tubes for lead and other metal contamination. Lead uptake by blood over time from the various tubes was minimal with the "low-lead" Vacutainer tubes and with all but four of the other tube types. In the large survey of Mahaffey et al. (1979), 5-ml Monoject (Sherwood) or 7-ml lavender-top Vacutainer (Becton-Dickinson) tubes were found satisfactory. However, when more precision is needed, tubes are best recleaned in the laboratory and lead-free anticoagulant added (although this would be less convenient for sampling efficiency than the commercial tubes). In addition, blank levels for every batch of samples should be verified.

9.2.1.2 Urine Sampling. Urine samples require collection in lead-free containers and caps as well as the addition of a low-lead bacteriocide if samples are to be stored for any period of time. While not always feasible, 24-hour samples should be obtained, as such collection would level out any effect of variation in excretion over time. If spot sampling is done, lead levels should be expressed per unit creatinine. For 24-hour collections, corrections must be made for urine density.

9.2.1.3 Hair Sampling. The usefulness of hair lead analysis depends on the manner of sampling. Hair samples should be removed from subjects by some consistent method, either by a predetermined length measured from the skin or by using the entire hair. Hair should be placed in air-tight containers for shipment or storage. For segmental analysis, the entire hair length is required.

9.2.1.4 Mineralized Tissue. An important consideration in deciduous tooth collection is consistency in the type of teeth collected from various subjects. Fosse and Justesen (1978) reported no difference in lead content between molars and incisors, and Chatman and Wilson (1975) reported comparable whole tooth levels for cuspids, incisors, and molars. On the other hand, Mackie et al. (1977) and Lockeretz (1975) noted levels varying with tooth type, with a

statistically significant difference (Mackie et al., 1977) between second molar (lowest levels) and incisors (highest levels). The fact that the former two studies found rather low overall lead levels across groups, while Mackie et al. (1977) reported higher values, suggests that dentition differences in lead content may be magnified at relatively higher levels of exposure. Delves et al. (1982), comparing pairs of central incisors or pairs of central and lateral incisors from the same child, found that lead levels may even vary within a specific type of tooth. These data suggest the desirability of acquiring two teeth per subject to get an average lead value.

Teeth containing fillings or extensive decay are best eliminated from analysis. Mackie et al. (1977) discarded decayed teeth if the extent of decay exceeded approximately 30 percent.

9.2.1.5 Sample Handling in the Laboratory. With blood samples, there is the potential problem of the effect of storage on the lead content. It is clear that dilute aqueous solutions of lead will surrender a sizable portion of the lead content to the container surface, whether glass or plastic (Issaq and Zielinski, 1974; Unger and Green, 1977); whether there is a comparable effect, or the extent of such an effect, with blood is not clear. Unger and Green (1977) claim that lead loss from blood to containers parallels that seen with aqueous solutions, but their data do not support this assertion. Moore and Meredith (1977) used isotopic lead spiking (^{203}Pb) with and without carrier in various containers at differing temperatures to monitor lead stability in blood over time. The only material loss occurred with soda glass at room temperature after 16 days. Nackowski et al. (1977) found that "low-lead" blood tubes, while quite satisfactory in terms of sample contamination, began to show transfer of lead to the container wall after four days. Meranger et al. (1981) studied movement of lead, spiked to various levels, to containers of various composition as a function of temperature and time. In all cases, reported lead loss to containers was significant. However, there are problems with the above reports. Spiked samples probably are not incorporated into the same biochemical environment as lead inserted *in vivo*. The Nackowski et al. (1977) study did not indicate whether the blood samples were kept frozen or refrigerated between testing intervals. Mitchell et al. (1972) found that the effect of blood storage depends on the method of analysis, with lower recoveries of lead from aged blood being seen using the Hessel (1968) method.

Lerner (1975) collected blood samples (35 originally) from a single subject into lead-free tubes and, after freezing, forwarded them in blind fashion to a certified testing laboratory over a period of 9 months. Four samples were lost, while one was rejected as being grossly contaminated (4 standard deviations from mean). Of the remaining 30 samples, the mean was 18.3 µg/dl with a standard deviation (S.D.) of 3.9. The analytical method had a precision of ±3.5 µg Pb/dl (1 = S.D.) at normal levels of lead, suggesting that the overall stability of the samples in terms of lead content was good. Boone et al. (1979), reported that samples

frozen for periods of less than a year showed no effect of storage, while Piscator (1982) noted no change in low levels (<10 µg/dl) when samples were stored at -20°C for 6 months. Based on the above data, it appears that blood samples to be stored for any period of time should be frozen rather than refrigerated, with care taken to prevent breaking of the tube during freezing. Teeth and hair samples, when stored in containers to minimize contamination, are indefinitely stable.

The actual site of analysis should be as lead-free as possible. Given the uncommon availability of an "ultra-clean" facility such as that described by Patterson and Settle (1976), the next desirable level of laboratory cleanliness is the "Class 100" facility, in which there are fewer than 100 airborne particles >0.5 µm. These facilities employ high efficiency particulate air filtering and laminar air flow (with movement away from sample handling areas). Totally inert surfaces in the working area and an antechamber for removing contaminated clothes, appliance cleaning, etc. are other necessary features.

All plastic and glass ware coming into contact with samples should be rigorously cleaned and stored away from dust contact; materials such as ashing vessels should permit minimal lead leaching. In this regard, Teflon and quartz ware is more desirable than other plastics or borosilicate glass (Patterson and Settle, 1976).

Reagents, particularly for chemical degradation of biological samples, should be both certified and periodically tested for retention of quality. Several commercial grades of reagents are available, although precise work may require doubly purified materials from the National Bureau of Standards. These reagents should be stored with a minimum of surface contamination around the top of the containers.

For a more detailed discussion of appropriate laboratory practices, the reader may consult LaFleur (1976).

9.2.2 Methods of Lead Analysis

Detailed technical discussion of the array of instruments available to measure lead in blood and other media is outside the scope of this Chapter (see Chapter 4). This discussion is structured more appropriately to those aspects of methodology dealing with relative sensitivity, specificity, accuracy and precision. While there is increasing acceptance of international standardized units (SI units) for expressing lead levels in various media, units familiar to clinicians and epidemiologists will be used here. (To convert µg Pb/dl blood to SI units (µmoles/liter), multiply by 0.048.)

Many reports over the years have purported to offer satisfactory analysis of lead in biological media, but in fact have shown rather meager adherence to criteria for accuracy and precision or have shown a lack of demonstrable utility across a wide spectrum of analytical applications. Therefore, discussion in this section is confined to "definitive" and reference

methods for lead analysis, except for a brief treatment of the traditional but now widely supplanted colorimetric method.

Using the definition of Cali and Reed (1976), a definitive method is one in which all major or significant parameters are related by solid evidence to the absolute mass of the element with a high degree of confidence. A reference method, by contrast, is one of demonstrated accuracy, validated by a definitive method and arrived at by consensus through performance testing by a number of different laboratories. In the case of lead in biological media, the definitive method is isotope-dilution mass spectrometry (IDMS). IDMS accuracy comes from the fact that all manipulations are on a weight basis involving simple procedures. The measurements entail only ratios and not the absolute determinations of the isotopes involved, which greatly reduces instrumental corrections or errors. Reproducible results to a precision of one part in 10^4 or 10^5 are routine with specially designed instruments.

In terms of reference methods for lead in biological media, such a label cannot technically be attached to atomic absorption spectrometry in its various instrumentation/methodology configurations or to the electrochemical technique, anodic stripping voltammetry. However, these have been termed reference methods insofar as their precision and accuracy can be verified or calibrated against IDMS.

Other methods that are recognized for trace metal analysis in general are not fully applicable to biological lead or have inherent shortcomings. X-ray fluorescence analysis lacks the requisite sensitivity for media with low lead content and the associated sample preparation may present a high contamination risk. A notable exception may be X-ray fluorescence analysis of teeth or bone in situ as discussed below. Neutron activation analysis is the method of choice with many elements, but is not technically feasible for lead analysis because of the absence of long-lived isotopes.

9.2.2.1 Lead Analysis in Whole Blood. The first generally accepted technique for quantifying lead in whole blood and other biological media was a colorimetric method that involved spectrophotometric measurement based on the binding of lead to a chromogenic agent to yield a chromophoric complex. The complexing agent has typically been dithizone, 1,5-diphenylthiocarbazone, yielding a lead complex that is spectrally measured at 510 nm.

Two variations of the spectrophotometric technique used when measuring low levels of lead have been the USPHS (National Academy of Sciences, 1972) and APHA (American Public Health Association, 1955) procedures. In both, venous blood or urine is wet ashed using concentrated nitric acid of low lead content followed by adjustment of the ash with hydroxylamine and sodium citrate to a pH of 9-10. Cyanide ion is added and the solution extracted with dithizone in chloroform. Back extraction removes the lead into dilute nitric acid; the acid layer is treated with ammonia, then cyanide, and re-extracted with dithizone in chloroform. The extracts are read in a spectrophotometer at 510 nm. Bismuth interference is handled (APHA

variation) by removal with dithizone at pH 3.4. According to Lerner (1975), the analytical precision in the "normal" range is about ±3.5 μg Pb/dl (1 = S.D.), using 5 ml of sample.

The most accurate and precise method for lead measurement in blood is isotope dilution mass spectrometry. As typified by the report of Machlan et al. (1976), whole blood samples are accurately weighed, and a weighed aliquot of ^{206}Pb-enriched isotope solution is added. After sample decomposition with ultra-pure nitric and perchloric acids, samples are evaporated, residues are taken up in dilute lead-free hydrochloric acid, and lead is isolated using anion-exchange columns. Column eluates are evaporated with the above acids, and lead is deposited onto high purity platinum wire from dilute perchloric acid. The $^{206}Pb/^{208}Pb$ ratio is then determined by thermal ionization mass spectrometry. Samples without added isotope and reagent blanks are also carried through the procedure. In terms of precision, the 95 percent confidence level for lead samples overall is within 0.15 percent. Due to the expense incurred by the requirements for operator expertise, the amount of time involved, and the high standard of laboratory cleanliness, IDMS is mainly of practical value in the development of standard reference materials and for the verification of other analytical methods.

Atomic absorption spectrometry (AAS) is widely used for lead measurements in whole blood, with sample analysis involving analysis of venous blood with chemical degradation, analysis of liquid samples with or without degradation, and samples applied to filter paper. It is thus the most flexible for samples already collected or subject to manipulation.

By means of a flame or electrothermal excitation, ionic lead in some matrix is first vaporized and then converted to the atomic state, followed by resonance absorption from either a hollow cathode or electrodeless discharge lamp generating lead absorption lines at 217.0 and 283.3 nm. After monochrometer separation and photomultiplier enhancement of the differential signal, it is measured electronically.

The earliest methods of atomic absorption spectrometric analysis involved the aspiration into a flame of ashed samples of blood, usually subsequent to extraction into an organic solvent to enhance sensitivity by preconcentration. Some methods did not involve digestion steps prior to solvent extraction (Kopito et al., 1974). Of these various flame AAS methods, that of Hessel's (1968) technique continues to be used with some frequency.

Currently, lead measurement in blood by AAS employs several different methods that permit greater sensitivity, precision, and economy of sample and time. The flame method of Delves (1970), called the "Delves cup" procedure, usually involves delivery of discrete small samples (≤100 μl) of unmodified whole blood to nickel cups, with subsequent drying and peroxide decomposition of organic content before positioning in the flame. The marked enhancement of sensitivity over conventional flame aspiration is due to immediate, total consumption of the sample and the generation of a localized population of atoms. In addition to discrete blood volumes, blood-containing filter paper disks have been used (Joselow and Bogden, 1972; Cernil

and Sayers, 1971; Piomelli et al., 1980). Several modifications of the Delves method include that of Ediger and Coleman (1972), in which dried blood samples in the cups are pre-ignited to destroy organic matter by placement near the flame in a precise, repeatable manner, and the variation of Barthel et al. (1973), in which blood samples are mixed with dilute nitric acid in the cups followed by drying in an oven at 200°C and charring at 450°C on a hot plate. A number of laboratories eschew even these modifications and follow dispensing and drying with direct placement of the cup into the flame (e.g., Mitchell et al., 1974). The Delves cup procedure may require correction for background spectral interference, which is usually achieved by instrumentation equipped at a non-resonance absorption line. While the 217.0 nm line of lead is less subject to such interference, precise work is best done with correction. This method as applied to whole blood lead appears to have an operational sensitivity down to 1.0 µg Pb/dl, or somewhat below when competently employed, and a relative precision of approximately 5 percent in the range of levels encountered in the United States.

AAS methods using electrothermal (furnace) excitation in lieu of a flame can be approximately 10-fold more sensitive than the Delves procedure. A number of reports describing whole blood lead analysis have appeared in the literature (Lawrence, 1982, 1983). Because of increased sensitivity, the "flameless" AAS technique permits the use of small blood volumes (1-5 µl) with samples undergoing drying and dry ashing in situ. Physicochemical and spectral interferences are inherently severe with this approach, requiring careful background correction. In one flameless AAS configuration, background correction exploits the Zeeman effect, where correction is made at the specific absorption line of the element and not over a band-pass region, as is the case with the deuterium arc. While control of background interference up to 1.5 molecular absorbence is claimed with the Zeeman system (Koizumi and Yasuda, 1976), it is technically preferable to employ charring before atomization. Hinderberger et al. (1981) used dilute ammonium phosphate solution to minimize chemical interference in their furnace AAS method.

Precision can be a problem in the flameless technique unless careful attention is paid to the problem of sample diffusibility over and into the graphite matrix of the receiving receptacle -- tube, cup, or rod. With the use of diluted samples and larger applied volumes, the relative precision of this method can approach that of the Delves technique (Delves, 1977).

In addition to the various atomic absorption spectral methods noted above, electrochemical techniques have been applied to blood lead analysis. Electrochemical methods, in theory, differ from AAS methods in that the latter are "concentration" methods regardless of sample volumes available, while electrochemical analysis involves bulk consumption of sample and hence would have infinite sensitivity, given an infinite sample volume. This intrinsic property is of little practical advantage given usual sample volume, instrumentation design, and blank limits.

The most widely used electrochemical method for lead measurement in whole blood and other biological media is anodic stripping voltammetry (ASV) which is also probably the most sensitive, as it involves an electrochemical preconcentration (deposition) step in the analysis (Matson and Roe, 1966; Matson et al., 1970). In this method, samples such as whole blood (50-100 µl), are preferably but not commonly wet ashed and reconstituted in dilute acid or made electro-available with metal exchange reagents. Using freshly prepared composite electrodes of mercury film deposited on carbon, lead is plated out from the solution for a specific amount of time and at a selected negative voltage. The plated lead is then reoxidized in the course of anodic sweeping, generating a current peak that may be recorded on a chart or displayed on commercial instruments as units of concentration (µg/dl).

One alternative to the time and space demands of wet ashing blood samples is the use of metal exchange reagents that displace lead from binding sites in blood by competitive binding (Morell and Giridhar, 1976; Lee and Meranger, 1980). In one commercial preparation, this reagent consists of a solution of calcium, chromium, and mercuric ions. Use of the metal exchange reagent adds a chemical step that must be carefully controlled for full recovery of lead from the sample.

The working detection limit of ASV for blood is comparable to that of the AAS flameless methods while the relative precision is best with prior sample degradation, approximately 5 percent, but less when the blood samples are run directly with the ion exchange reagents (Morrell and Giridhar, 1976), particularly at the low end of "normal" blood lead values. While AAS methods require attention to various spectral interferences to achieve satisfactory performance, electrochemical methods such as ASV require consideration of such factors as the effects of co-reducible metals and agents that complex lead and alter its reduction-oxidation (redox) potential properties. Chelants used in therapy, particularly penicillamine, may interfere, as does blood copper, which may be elevated in pregnancy and such disease states as leukemia, lymphoma, and hyperthyroidism (Berman, 1981). At very low levels of lead in blood, then, ASV may pose more problems than atomic absorption spectrometric techniques.

Correction of whole blood lead values for hematocrit, although carried out in the past, is probably not appropriate and not commonly done at present. While the erythrocyte is the carrier for virtually all lead in blood, the saturation capacity of the red blood cell for lead is so high that it can still carry lead even at highly toxic levels (Kochen and Greener, 1973). Kochen and Greener (1973) also showed that acute or chronic dosing at a given lead level in rats with a wide range of hematocrits (induced by bleeding) gave similar blood lead values. Rosen et al. (1974), based on studies of hematocrit, plasma, and whole blood lead in children, noted hematocrit correction was not necessary, a view supported by Chisolm (1974).

9.2.2.2 Lead in Plasma. While virtually all of the lead present in whole blood is bound to the erythrocyte (Robinson et al., 1958; Kochen and Greener, 1973), lead in plasma is transported to affected tissues. It is very important, therefore, that every precaution be taken

to use non-hemolyzed blood samples for plasma isolation. The very low levels of lead in plasma require that more attention be paid to "ultra clean" methods.

Rosen et al. (1974) used flameless atomic absorption spectrometry and microliter samples of plasma to measure plasma lead, with background correction for the smoke signal generated for the unmodified sample. Cavalleri et al. (1978) used a combination of solvent extraction of modified plasma with preconcentrating and flameless atomic absorption. These authors noted that the method used by Rosen et al. (1974) permitted less precision and accuracy than did their technique, because a significantly smaller amount of lead was delivered to the furnace accessory.

DeSilva (1981) used a technique similar to that of Cavalleri et al. (1978), but collected samples in heparinized tubes, claiming that the use of EDTA as anticoagulant disturbs the cell-plasma distribution of lead enough to yield erroneous data. Much more care was given in this procedure to background contamination. In both cases, increasing levels of plasma lead were measured with increasing whole blood lead, suggesting an equilibrium ratio in contradiction to the data of Rosen et al. (1974), who found a fixed level of 2-3 µg Pb/dl plasma over a wide range of blood lead. However, the actual levels of lead in plasma in the DeSilva (1981) study were much lower than those reported by Cavalleri et al. (1978).

Using isotope-dilution mass spectrometry and sample collection/manipulation in an "ultra-clean" facility, Everson and Patterson (1980) measured the plasma lead levels in two subjects, a control and a lead-exposed worker. The control had a plasma lead level of 0.002 µg Pb/dl, several orders of magnitude lower than that seen with studies using less precise analytical approaches. The lead-exposed worker had a plasma level of 0.2 µg Pb/dl. Several other reports in the literature using isotope-dilution mass spectrometry noted somewhat higher values of plasma lead (Manton and Cook, 1979; Rabinowitz et al., 1974), which Everson and Patterson (1980) have ascribed to problems of laboratory contamination. Utilizing tracer lead to minimize the impact of contamination results in a value of 0.15 µg/dl (Rabinowitz et al., 1974).

With appropriate plasma lead methodology, reported lead levels are extremely low, the degree varying with the methods used to measure such concentrations. While the data of Everson and Patterson (1980) were obtained from only two subjects, it seems unlikely that using more subjects would result in a plasma lead range extending upward to the levels seen with ordinary methodology in ordinary laboratory surroundings. The above considerations are necessary when discussing appropriate methodology for plasma analysis, and the Everson and Patterson (1980) report indicates that some doubt surrounds results obtained with conventional methods. Although not the primary focus of their study, the values obtained by Everson and Patterson (1980) for whole blood lead, unlike the data for plasma, are within the ranges for unexposed (11 µg Pb/dl) and exposed (80 µg Pb/dl) subjects generally reported with other methods. This

would suggest that, for the most part, reported values do actually reflect in vivo blood lead levels rather than sampling problems or inaccurate methods.

9.2.2.3 Lead in Teeth. When carrying out analysis of shed deciduous or extracted permanent teeth, some reports have used the whole tooth after surface cleaning to remove contaminating lead (e.g., Moore et al., 1978; Fosse and Justesen, 1978; Mackie et al., 1977), while others have measured lead in dentine (e.g., Shapiro et al., 1973; Needleman et al., 1979; Al-Naimi et al., 1980). Several reports (Grandjean et al., 1978; Shapiro et al., 1973) have also described the analysis of secondary (circumpulpal) dentine, that portion of the tooth found to have the highest relative fraction of lead. Needleman et al. (1979) separated dentine by embedding the tooth in wax, followed by thin central sagittal sectioning. The dentine was then isolated from the sawed sections by careful chiseling.

The mineral and organic composition of teeth and their components requires the use of thorough chemical decomposition techniques, including wet ashing and dry ashing steps, sample pulverizing or grinding, etc. In the procedure of Steenhout and Pourtois (1981), teeth are dry ashed at 450°C, powdered, and dry ashed again. The powder is then dissolved in nitric acid. Fosse and Justesen (1978) reduced tooth samples to a coarse powder by crushing in a vise, followed by acid dissolution. Oehme and Lund (1978) crushed samples to a fine powder in an agate mortar and dissolved the samples in nitric acid. Mackie et al. (1977) and Moore et al. (1978) dissolved samples directly in concentrated acids. Chatman and Wilson (1975) and Needleman et al. (1974) carried out wet ashing with nitric acid followed by dry ashing at 450°C. Oehme and Lund (1978) found that acid wet ashing of tooth samples yielded better results if carried out in a heated Teflon bomb at 200°C.

With regard to methods of measuring lead in teeth, atomic absorption spectrometry and anodic stripping voltammetry have been employed most often. With the AAS methods, the high mineral content of teeth tends to argue for isolating lead from this matrix before analysis. In Needleman et al.'s (1974) and Chatman and Wilson's (1975) method, ashed residues in nitric acid were treated with ammonium nitrate and ammonium hydroxide to a pH of 2.8, followed by dilution and extraction with a methylisobutylketone solution of ammonium pyrrolidinecarbodithioate. Analysis is by flame AAS using the 217.0 nm lead absorption line. A similar procedure was employed by Fosse and Justesen (1978).

Anodic stripping voltammetry has been successfully used in tooth lead measurement (Shapiro et al., 1973; Needleman et al., 1979; Oehme and Lund, 1978). As typified by the method of Shapiro et al. (1973), samples of dentine were dissolved in a small volume of low-lead concentrated perchloric acid and diluted (5.0 ml) with lead-free sodium acetate solution. With deoxygenation, samples were analyzed in a commercial ASV unit, using a plating time of 10 minutes at a plating potential of -1.05 V. Anodic sweeping was at a rate of 60 mV/sec with a variable current of 100-500 μA.

Since lead content of teeth is higher than in most samples of biological media, the relative precision of analysis with appropriate accommodation of the matrix effect, such as the use of matrix-matched standards, in the better studies indicates a value of approximately 5-7 percent.

All of the above methods involve shed or extracted teeth and consequently provide a retrospective determination of lead exposure. In Bloch et al.'s (1976) procedure, tooth lead is measured in situ using an X-ray fluorescence technique. A collimated beam of radiation from ^{57}Co was allowed to irradiate the upper central incisor teeth of the subject. Using a relatively safe 100-second irradiation time and measurement of $K_{\alpha 1}$ and $K_{\alpha 2}$ lead lines via a germanium diode and a pulse height analyzer for signal processing, lead levels of 15 ppm or higher could be measured. Multiple measurement by this method would be very useful in prospective studies because it would show the "on-going" rate of increase in body lead burden. Furthermore, when combined with serial blood sampling, it would provide data for blood lead-tooth lead relationships.

9.2.2.4 Lead in Hair. Hair constitutes a non-invasive sampling source with virtually no problems with sample stability on extended storage. However, the advantages of accessibility and stability are offset by the problem of assessing external contamination of the hair surface by atmospheric fallout, hand dirt, lead in hair preparations, etc. Thus, such samples are probably of less value overall than those from other media.

The various methods that have been employed for removal of external lead have been reviewed (Chatt et al., 1980; Gibson, 1980; Chattopadhyay et al., 1977). Cleaning techniques obviously should be vigorous enough to remove surface lead but not so vigorous as to remove the endogenous fraction. To date, it remains to be demonstrated that any published cleaning procedure is reliable enough to permit acceptance of reported levels of lead in hair. Such a demonstration would have to use lead isotopic studies with both surface and endogenous isotopic lead removal monitored as a function of a particular cleaning technique.

9.2.2.5 Lead in Urine. Analysis of lead in urine is complicated by its relatively low concentrations (lower than in blood in many cases) as well as by the complex mixture of mineral elements present. Lead levels are higher, of course, in cases where lead mobilization or therapy with chelants is in progress, but in these cases samples must be analyzed to account for lead bound to chelants such as EDTA. This requires either sample ashing or the use of standards containing the chelant. Although analytical methods have been published for the direct analysis of lead in urine, samples are probably best wet ashed before analysis, using the usual mixtures of nitric plus sulfuric and/or perchloric acids.

Both atomic absorption spectrometric and anodic stripping voltammetric methods have been applied to urine lead analyses, the former employing either direct analysis of ashed residues or a preliminary chelation-extraction step. With flame AAS, ashed urine samples must invari-

ably be extracted with a chelant such as ammonium pyrrolidinecarbodithioate in methylisobutylketone to achieve reasonably satisfactory results. Direct analysis, furthermore, creates mechanical problems with burner operation, due to the high mineral content of urine, and results in considerable maintenance problems with equipment. The procedure of Lauwerys et al. (1975) is typical of flame AAS methods with preliminary lead separation. Owing to the relatively greater sensitivity of graphite furnace (flameless) AAS, this variation of the method has been applied to urine analysis in scattered reports where it appears that adequate performance for direct sample analysis requires steps to minimize matrix interference. A typical example of one of the better direct analysis methods is that of Hodges and Skelding (1981). Urine samples were mixed with iodine solution and heated, then diluted with a special reagent containing ammonium molybdate, phosphoric acid, and ascorbic acid. Small aliquots (5 µl) were delivered to the furnace accessory of an AAS unit containing a graphite tube pretreated with ammonium molybdate. The relative standard deviation of the method is reported to be about 6 percent. In the method of Legotte et al. (1980), such tube treatment and sample modifications were not employed and the average precision figure was 13 percent.

Compared with various atomic absorption spectrometric methods, anodic stripping voltammetry has been less frequently employed for urine lead analysis, and it would appear from available electrochemical methods in general that such techniques applied to urine require further development. Franke and de Zeeuw (1977) used differential pulse anodic stripping voltammetry as a screening tool for lead and other elements in urine. Jagner et al. (1979) described analysis of urine lead using potentiometric stripping. In their procedure the element was pre-concentrated at a thin-film mercury electrode as in conventional ASV, but deoxygenated samples were reoxidized with either oxygen or mercuric ions after the circuitry was disconnected.

As noted in Section 9.1.1.2, spot sampling of lead in urine should be expressed per unit creatinine, if it is not possible to obtain 24-hour collection.

9.2.2.6 Lead in Other Tissues. Bone samples of experimental animal or human autopsy origin require preliminary cleaning procedures for removal of muscle and connective tissue, with care being taken to minimize sample contamination. As is the case with teeth, samples must be chemically decomposed before analysis. Satisfactory instrumental methods for bone lead analysis comprise a much smaller literature than is the case for other media.

Wittmers et al. (1981) have described the measurement of lead in dry-ashed (450°C) bone samples using flameless atomic absorption spectrometry. Ashed samples were weighed and dissolved in dilute nitric acid containing lanthanum ion, the latter being used to suppress interference from bone elements. Small volumes (20 µl) and high calcium content required that atomization be done at 2400°C to avoid condensation of calcium within the furnace. Quantification was by the method of additions. Relative precision was 6-8 percent at relatively high lead content (60 µg/g ash) and 10-12 percent at levels of 14 µg/g ash or less.

Ahlgren et al. (1980) described the application of X-ray fluorescence analysis to *in vivo* lead measurement in the human skeleton, using tibia and phalanges. In this technique, irradiation is carried out with dual ^{57}Co gamma ray source. The generated $K_{\alpha 1}$ and $K_{\alpha 2}$ lead lines are detected with a lithium-drifted germanium detector. The detection limit is 20 parts per million.

Soft organs differ from other biological media in the extent of anatomic heterogeneity as well as lead distribution, e.g., brain vs. kidney. Hence, sample analysis involves either discrete regional sampling or the homogenizing of an organ. The efficiency of the latter can vary considerably, depending on the density of the homogenate, the efficiency of rupture of the formed elements, and other factors. Glass-on-glass homogenizing is to be avoided because lead is liberated from the glass matrix with abrasion.

Atomic absorption spectrometry, in its flame or flameless variations, appears to be the method of choice in many studies. In the procedure of Slavin et al. (1975), tissues were wet ashed and the residues taken up in dilute acid and analyzed with the furnace accessory of an AAS unit. A large number of reports representing slight variations of this basic technique have appeared over the years (Lawrence, 1982, 1983). Flame procedures, being less sensitive than the graphite furnace method, require more sample than may be available or are restricted to measurement in tissues where levels are relatively high, e.g., kidney. In the method of Farris et al. (1978), samples of brain, liver, lung, or spleen (as discrete segments) were lyophilized and solubilized at room temperature with nitric acid. Following neutralization, lead was extracted into methylisobutylketone with ammonium pyrrolidinecarbodithioate and aspirated into the flame of an AAS unit. The reported relative precision was 8 percent.

9.2.3 Quality Assurance Procedures In Lead Analysis

Regardless of technical differences among the different methodologies for lead analysis, one can define the quality of such techniques as being of: (1) poor accuracy and poor precision; (2) poor accuracy and good precision; or (3) good accuracy and good precision. In terms of available information, the major focus in assessing quality has been on blood lead determinations.

According to Boutwell (1976), the use of quality control testing for lead measurement rests on four assumptions: (1) the validity of the specific procedure for lead in some matrix has been established; (2) the stability of the factors making up the method has been both established and manageable; (3) the validity of the calibration process and the calibrators with respect to the media being analyzed has been established; and (4) surrogate quality control materials of reliably determined analyte content can be provided. These assumptions, when translated into practice, revolve around steps employed within the laboratory, using a battery of "internal checks" and a further reliance on "external checks" such as a formal, well-organized, multi-laboratory proficiency testing program.

Analytical quality protocols can be further divided into start-up and routine procedures, the former entailing the establishment of detection limits, "within-run" and "between-run" precision, recovery of analyte, etc. When a new method is adopted for some specific analytical advantage, the procedure is usually tested in the laboratory or outside the laboratory for comparative performance. For example, Hicks et al. (1973) and Kubasik et al. (1972) reported that flameless techniques for measuring lead in whole blood were found to have a satisfactory correlation with results using conventional flame procedures. Matson et al. (1970) noted a good agreement between anodic stripping voltammetry and both atomic absorption spectral and dithizone colorimetric techniques. The problem with such comparisons is that the reference method is assumed to be accurate for the particular level of lead in a given matrix. High correlations obtained in this manner may simply indicate that two inaccurate methods are simultaneously performing with the same level of precision.

Preferable approaches for assessing accuracy are the use of certified samples determined by a definitive method, or a direct comparison of different techniques with a definitive procedure. For example, Eller and Hartz (1977) compared the precision and accuracy of five available methods for measuring lead in blood: dithizone spectrometry, extraction and tantalum boat AAS, extraction and flame aspiration AAS, direct aspiration AAS, and graphite furnace AAS techniques. Porcine whole blood certified by the National Bureau of Standards (NBS) using isotope-dilution mass spectrometry at 1.00 μg Pb/g (±0.023) was tested and all methods were found to be equally accurate. The tantalum boat technique was found to be the least precise. The obvious limitation of these data is that they relate to a high blood lead content, suitable for use in measuring the exposure of lead workers or in some other occupational context, but less appropriate for clinical or epidemiological investigations.

Boone et al. (1979) compared the analytical performance of 113 laboratories using various methods and 12 whole blood samples (blood from cows fed a lead salt) certified as to lead content using isotope-dilution mass spectrometry at the NBS. Lead content ranged from 13 to 102 μg Pb/dl, determined by anodic stripping voltammetry and five variations of AAS. The order of agreement with NBS values, i.e., relative accuracy, was: extraction > ASV > tantalum strip > graphite furnace > Delves cup > carbon rod. The AAS methods all tended to show bias, being positive at values less than 40 μg Pb/dl and negative at levels greater than 50 μg Pb/dl. ASV tended to show less of a positive bias problem, although it was not bias-free within either of the blood lead ranges. In terms of relative precision, the ranking was: ASV > Delves cup > tantalum strip > graphite furnace > extraction > carbon rod. The overall ranking in accuracy and precision indicated: ASV > Delves cup > extraction > tantalum strip > graphite furnace > carbon rod. As the authors cautioned, the above data should not be taken to indicate that any established laboratory using one particular technique would not perform better than this; rather, it should be used as a guide for newer facilities choosing among methods.

There are a number of necessary steps in quality assurance pertinent to the routine measurement of lead that should be used in an ongoing program. With respect to internal checks of routine performance, these include calibration and precision and accuracy testing. With biological matrices, the use of matrix-matched standards is quite important, as is an understanding of the range of linearity and variation of calibration curve slopes from day to day. It is common practice to analyze a given sample in duplicate, further replication being carried out if the first two determinations vary beyond a predetermined range. A second desirable step is the analysis of samples collected in duplicate but analyzed "blind" to avoid bias.

Monitoring of accuracy within the laboratory is limited to the availability of control samples having a certified lead content in the same medium as the samples being analyzed. Controls should be as physically close to the media being analyzed as possible. Standard reference materials (SRMs), such as orchard leaves and lyophilized bovine liver, are of help in some cases, but there is need for NBS-certified blood samples for the general laboratory community. There are commercially available whole blood samples, prepared and certified by the marketing facility (TOX-EL, A.R. Smith Co., Los Angeles, CA; Kaulson Laboratories, Caldwell, NJ; Behringwerke AG, Marburg, W. Germany; and Health Research Institute, Albany, NY). With these samples, attention must be paid to the reliability of the methods used by reference laboratories. The use of such materials, from whatever source, must minimize bias; for example, the attention given control specimens should be the same as that given routine samples.

Finally, the most important form of quality assurance is the ongoing assessment of laboratory performance by proficiency testing programs using externally provided specimens for analysis. Earlier interlaboratory surveys of lead measurement in blood and in urine indicated that a number of laboratories had performed unsatisfactorily, even at high levels of lead (Keppler et al., 1970; Donovan et al., 1971; Berlin et al., 1973), although there may have been problems in the preparation and status of the blood samples during and after distribution (World Health Organization, 1977). These earlier tests for proficiency indicated that: (1) many laboratories were able to achieve a good degree of precision within their own facilities; (2) the greater the number of samples routinely analyzed by a facility, the better the performance; and (3) 30 percent of the laboratories routinely analyzing blood lead reported values differing by more than 15 percent from the true level (Pierce et al., 1976).

In the more recent, but very limited, study of Paulev et al. (1978), five facilities participated in a survey, using samples to which known amounts of lead were added. For lead in both whole blood and urine, the interlaboratory coefficient of variation was reported to be satisfactory, ranging from 12.3 to 17.2 percent for blood and urine samples. Aside from its

limitation of scope, this study used "spiked" instead of in vivo lead, so that extraction techniques used in most of the laboratories surveyed would have given misleadingly better results in terms of actual recovery.

Maher et al. (1979) described the outcome of a proficiency study involving up to 38 laboratories that analyzed whole blood pooled from a large number of samples submitted for blood lead testing. The Delves cup technique was the most heavily represented, followed by the chelation-extraction plus flame AAS method and the graphite furnace AAS method. Anodic stripping voltammetry was used by only approximately 10 percent of the laboratories, so that the results basically portray AAS methods. All laboratories had about the same degree of accuracy, with no evidence of consistent bias, while the interlaboratory coefficient of variation was approximately 15 percent. A subset of this group, certified by the American Industrial Hygiene Association (AIHA) for air lead, showed a corresponding precision figure of approximately 7 percent. Over time, the subset of AIHA-certified laboratories remained about the same in proficiency, while the other facilities showed continued improvement in both accuracy and precision. This study indicates that program participation does help the performance of a laboratory doing blood lead determinations.

The most comprehensive proficiency testing program is that carried out by the Centers for Disease Control of the U.S. Public Health Service. This consists of two operationally and administratively distinct subprograms, one conducted by the Center for Environmental Health (CEH) and the other by the Licensure and Proficiency Testing Division, Laboratory Improvement Program Office (LIPO). The CEH program is directed at facilities involved in lead poisoning prevention and screening, while LIPO is concerned with laboratories seeking certification under the Clinical Laboratories Improvement Act of 1967 as well as under regulations of the Occupational Safety and Health Administration (OSHA). Both the CEH and LIPO protocols involve the use of bovine whole blood certified as to content by reference laboratories (6 in the CEH program, 20-23 in LIPO) with an ad hoc target range of ±6 μg Pb/dl for values of 40 μg Pb/dl or less and ±15 percent for higher levels. Three samples are provided monthly from CEH, for a total of 36 yearly, while LIPO participants receive 3 samples quarterly (12 samples yearly). Use of a fixed range rather than a standard deviation has the advantage of allowing the monitoring of overall laboratory improvement.

For Fiscal Year (FY) 1981, 114 facilities were in the CEH program, 92 of them participating for the entire year. Of these, 57 percent each month reported all three samples within the target range, and 85 percent on average reported two out of three samples correctly. Of the facilities reporting throughout the year, 95 percent had a 50 percent or better performance, i.e., 18 blood samples or better. If one compares these summary data for FY 1981 with earlier annual reports, it would appear that there has been considerable improvement in the

number of laboratories achieving higher levels of proficiency. For the interval FY 1977-79, there was a 20 percent increase in the number correctly analyzing more than 80 percent of all samples and a 33 percent decrease in those reporting less than 50 percent correct. In the last several years, FY 1979-81, overall performance appears to have more or less stabilized.

With the LIPO program for 1981 (Dudley, 1982), the overall laboratory performance averaged across all quarters was 65 percent of the laboratories analyzing all samples correctly and approximately 80 percent performing well with two of three samples. Over the four years of this program, an increasing ability to correctly analyze lead in blood appears to have been demonstrated. Dudley's survey (1982) also indicates that reference laboratories in the LIPO program are becoming more accurate relative to isotope-dilution mass spectrometry values, i.e., bias over the blood lead range is contracting.

Current OSHA criteria for certification of laboratories measuring occupational blood lead levels require that eight of nine samples be correctly analyzed in the previous quarter (U.S. Occupational Safety and Health Administration, 1982). These criteria appear to reflect the ability of a number of laboratories to perform at this level.

It should be noted that most proficiency programs, including the CEH and LIPO surveys, are appropriately concerned with blood lead levels encountered in such cases as pediatric screening for excessive exposure to lead or in occupational exposures. As a consequence, there does appear to be an underrepresentation of lead values in the low end of the "normal" range. In the CEH distribution for FY 1981, four samples (11 percent) were below 25 μg Pb/dl. The relative performance of the 114 facilities with these samples indicates outcomes much better than with the whole sample range.

9.3 DETERMINATION OF ERYTHROCYTE PORPHYRIN (FREE ERYTHROCYTE PROTOPORPHYRIN, ZINC PROTOPORPHYRIN)

9.3.1 Methods of Erythrocyte Porphyrin Analysis

Lead exposure results in inhibition of the final step in heme biosynthesis, the insertion of iron into protoporphyrin IX to form heme. This leads to an accumulation of the porphyrin, with zinc (II) occupying the position normally filled by iron. Depending on the particular method of analysis, zinc protoporphyrin (ZPP) itself or the metal-free form, free erythrocyte protoporphyrin (FEP), is measured. FEP generated as a consequence of chemical manipulation should be kept distinct from the metal-free form biochemically produced in the porphyria, erythropoietic protoporphyria. The chemical or "wet" methods measure free erythrocyte porphyrin or zinc protoporphyrin, depending upon the relative acidity of the extraction medium. The hematofluorometer in its commercially available form measures zinc protoporphyrin.

Porphyrins are labile due to photochemical decomposition; hence, samples must be protected from light during collection and handling and analyzed as soon as possible. Hematocrits must also be obtained to adjust for anemic subjects.

In terms of methodological approaches for EP analysis, virtually all methods now in use exploit the ability of porphyrins to undergo intense fluorescence when excited at the appropriate wavelength of light. Such fluorometric techniques can be further classified as wet chemical micromethods or as micro methods using a recently developed instrument, the hematofluorometer. The latter involves direct measurement in whole blood. Because the mammalian erythrocyte contains all of the EP in whole blood, either packed cells or whole blood may be used, although the latter is more expedient.

Due to the relatively high sensitivity of fluorometric measurement for FEP or ZPP, laboratory methods for spectrofluorometric analysis require a relatively small sample of blood; hence, microtechniques are currently the most popular in most laboratories. These involve either liquid samples or blood collected on filter paper, the latter of use particularly in field sampling.

As noted above, chemical methods for EP analysis measure either free erythrocyte protoporphyrin, where zinc is chemically removed, or zinc protoporphyrin, where zinc is retained. The procedures of Piomelli and Davidow (1972), Granick et al., (1972), and Chisholm and Brown (1975) typify "free" EP methods, while those of Lamola et al. (1975), Joselow and Flores (1977), and Chisholm and Brown (1979) involve measurement of zinc-EP.

In Piomelli and Davidow's (1972) micro procedure, small volumes of whole blood, analyzed either directly or after collection on filter paper, were treated with a suspension of Celite in saline followed by a 4:1 mixture of ethyl acetate to glacial acetic acid. After agitation and centrifugation, the supernatant was extracted with 1.5N HCl. The acid layer was analyzed fluorometrically using an excitation wavelength of 405 nm and measurement at 615 nm. Blood collected on filter paper discs was first eluted with 0.2 ml H_2O. The filter paper method was found to work just as well as liquid samples of whole blood. Protoporphyrin IX was employed as a quantitative standard. Granick et al. (1972) use similar microprocedure, but it differs in the concentration of acid employed and the use of a ratio of maxima.

In Chisolm and Brown's (1975) variation, volumes of 20 µl of whole blood were treated with ethyl acetate/acetic acid (3:1) and briefly mixed. The acid extraction step was done with 3N HCl, followed by a further dilution step with more acid if the value was beyond the range of the calibration curve. In this procedure, protoporphyrin IX was used as the working standard, with coproporphyrin used to monitor the calibration of the fluorometer and any variance with the protoporphyrin standard.

The above microfluorometric methods all involve double extraction. In the single-extraction variation of Orfanos et al. (1977), liquid samples of whole blood (40 µl) or blood on filter paper were treated with acidified ethanol, the mixtures agitated and centrifuged, and the supernatants analyzed directly in fluorometer cuvettes. For blood samples on filter paper, blood was first leached from the paper with saline by soaking for 60 minutes. Coproporphyrin was used as the quantitative standard. The correlation coefficient with the Piomelli and Davidow (1972) procedure (see above) over the range 40-650 µg EP/dl RBCs was $r = 0.98$.

Lamola et al. (1975) analyzed the zinc protophyrin as such in their procedure. Small volumes of blood (20 µl) were worked up in a detergent (dimethyl dodecylamine oxide) and phosphate buffer solution, and fluorescence measured at 594 nm with excitation at 424 nm. In the variation of Joselow and Flores (1977), 10 µl of whole blood was diluted 1000-fold, along with protoporphyrin (Zn) standards, with the detergent-buffer solution. It should be noted that it is virtually impossible to obtain the ZPP standard in pure form, and Chisolm and Brown (1979) reported the use of protoporphyrin IX plus very pure zinc salt for such standards.

Regardless of the extraction methods used, some instrumental parameters are of importance, including the variation between cut-offs in secondary emission filters and variation among photomultiplier tubes in the red region of the spectrum. Hanna et al. (1976) compared four micromethods for EP analysis: double extraction with ethyl acetate/acetic acid and HCl (Piomelli and Davidow, 1972), single extraction with either ethanol or acetone (Chisolm et al., 1974), and direct solubilization with detergent (Lamola et al., 1975). Of these, the ethyl acetate and ethanol procedures were satisfactory; complete extraction occurred only with the ethylacetate/acetic acid method. In the method of Chisholm et al. (1974), it appears that the choice of acid and its concentration is more significant than the choice of organic solvent.

The levels of precision with these wet micromethods appears to differ with the specifics of analysis. Piomelli (1973) reported a coefficient of variation (C.V.) of 5 percent, compared to Herber's (1980) observation of 2-4 percent for the methods per se and 6-11 percent total C.V., which included precision of samples, standards, and day-to-day variation. The Lamola et al. (1975) method for ZPP measurement was found to have a C.V. of 10 percent (same day, presumably), whereas Herber (1980) reported a day-to-day C.V. of 9.3-44.6 percent. Herber (1980) also found that the wet chemical micro method of Piomelli (1973) had a detection limit of 20 µg EP/dl whole blood, while that of Lamola et al. (1975) was sensitive to 50 µg EP/dl whole blood.

The recent development of direct instrumental measurement of ZPP with the hematofluorometer has added a dimension to the use of EP measurement for field screening the lead exposure of large groups of subjects. As originally developed by Bell Laboratories (Blumberg et al., 1977) and now produced commercially, the apparatus employs front-face optics, in which excitation of the fluorophore is at an acute angle to the sample surface, with emitted light emerging from the same surface and thus being detected. Routine calibration requires a stable fluorescing material with spectra comparable to ZPP; the triphenylmethane dye Rhodamine B is used for this purpose. Absolute calibration requires adjusting the microprocessor-controlled readout system to read the known concentration of ZPP in reference blood samples, the latter calibration being performed as frequently as possible.

Hematofluorometers are designed for the measurement of EP in samples containing oxyhemoglobin, i.e., capillary blood. Venous blood, therefore, must first be oxygenated, usually by moderate shaking for approximately 10 minutes (Blumberg et al., 1977; Grandjean and Lintrup, 1978). A second problem with hematofluorometer use, in contrast to wet chemical methods, is interference by bilirubin (Karacic et al., 1980; Grandjean and Lintrup, 1978); this would occur with relatively low levels of EP. At levels normally encountered in lead workers or subjects with anemia or nonoccupational lead exposure, the degree of such interference is not considered significant (Grandjean and Lintrup, 1978). Karacic et al. (1980) have found that carboxyhemoglobin (COHb) may pose a potential problem, but its relevance to EP levels of subjects exposed to lead has not been fully elucidated. Background fluorescence in cover glass may be a problem and should be tested in advance. Finally, the accuracy of the hematofluorometer appears to be affected by hemolyzed blood.

Competently employed, the hematofluorometer appears to be reasonably precise but its accuracy may still be biased (see below). Blumberg et al. (1977) reported a C.V. of 3 percent over the entire range of ZPP values measured when using a prototype apparatus. Karacic et al. (1980) found the relative standard deviation to vary from 1 percent (0.92 mM ZPP/M Hb) to 5 percent (0.41 mM ZPP/M Hb) depending on concentration. Grandjean and Lintrup (1978) obtained a day-to-day C.V. of 5 percent using blood samples refrigerated for up to 9 weeks. Herber (1980) obtained a total C.V. of 4.1-11.5 percent.

A number of investigators have compared EP measured by the hematofluorometer with the laboratory or wet chemical techniques, ranging from a single, intralaboratory comparison to interlaboratory performance testing. The latter included the EP proficiency testing program of the Centers for Disease Control. Working with prototype instrumentation, Blumberg et al. (1977) obtained correlation coefficients of $r = 0.98$ (range: 50-800 µg EP/dl RBCs) and 0.99 (range: up to 1000 µg EP/dl RBCs) for comparisons with the Granick and Piomelli methods, respectively. Grandjean and Lintrup (1978), Castoldi et al. (1979) and Karacić et al. (1980) have achieved equally good correlation results.

Several reports (Culbreth et al., 1979; Scoble et al., 1981; Smith et al., 1980) have described the application of high-performance liquid chromatography (HPLC) to the analysis of either free or zinc protoporphyrin in whole blood. In one of the studies (Scoble et al., 1981), the protoporphyrins as well as coproporphyrin and mesoporphyrin IX were reported to be determined on-line fluorometrically in less than 6 minutes using 0.1 ml of blood sample. The HPLC approach remains to be tested in interlaboratory proficiency programs.

9.3.2 Interlaboratory Testing of Accuracy and Precision in EP Measurement

In a relatively early attempt to assess interlaboratory proficiency in EP measurement, Jackson (1978) reported results of a survey of 65 facilities that analyzed 10 whole blood samples by direct measurement with the hematofluorometer or by one of the wet chemical methods. In this survey, the instrumental methods had a low bias compared to the extraction techniques but tended to show better interlaboratory correlation.

At present, CDC's ongoing EP proficiency testing program constitutes the most comprehensive assessment of laboratory performance (U.S. Centers for Disease Control, 1981). Every month, three samples of whole blood prepared at the University of Wisconsin Laboratory of Hygiene are forwarded to participants. Reference means are determined by a group of reference laboratories with a target range of ±15 percent across the whole range of EP values. For Fiscal Year 1981, of the 198 laboratories participating, 139 facilities were involved for the entire year. Three of the 36 samples in the year were not included. Of the 139 year-long participants, 93.5 percent had better than half of the samples within the target range, 84.2 percent performed satisfactorily with 70 percent or more of the samples within range, and 50.4 percent of all laboratories had 90 percent or more of the samples yielding the correct results. The participants as a whole showed greater proficiency than in the previous year. Of the various methods currently used, the hematofluorometer direct measurement technique was most heavily represented. For example, the January 1982 survey of the three major techniques 154 participants used the hematofluorometer, 30 used the Piomelli method, and 7 used the Chisolm/Brown method.

The recent survey of Balamut et al. (1982) raises the troublesome observation that the use of commercially available hematofluorometers may yield satisfactory proficiency results but still be inaccurate when compared to the wet chemical method using freshly-drawn whole blood. Two hematofluorometers in wide use performed well in proficiency testing but showed an approximately 30 percent negative bias with clinical samples analyzed by both instrument and chemical microtechniques. This bias leads to false negatives when used in screening. It appears that periodic testing of split samples by both fluorometer and chemical means is necessary to monitor, and correct for, instrument negative bias. The basis of the bias is much more than can be explained by the difference between FEP and ZZP.

9.4 MEASUREMENT OF URINARY COPROPORPHYRIN

The elevation of urinary coproporphyrin (CP-U) with lead intoxication served as a useful indicator of such intoxication in children and lead workers for many years. Although analysis of CP-U has declined considerably in recent times with the development of other testing methods, such as measurement of erythrocyte protoporphyrin, it still possesses the advantage of showing active intoxication (Piomelli and Graziano, 1980).

The standard method of CP-U determination is the fluorometric procedure described by Schwartz et al. (1951). Urine samples are treated with acetate buffer and aqueous iodine, the latter converting coproporphyrinogen to CP. The porphyrin is partitioned into ethyl acetate and back-extracted (4 X) with 1.5N HCl. Coproporphyrin is employed as the quantitative standard. Working curves are linear below 5 µg CP/l urine.

In the absorption spectrometric technique of Haeger-Aronsen (1960), iodine is also used to convert coproporphyrinogen to CP. The extractant is ethyl ether, from which the CP is removed with 0.1N HCl. Absorption is read at three wavelengths, 380, 430, and the Soret maximum at 402 nm; and quantification is carried out using an equation involving the three wave lengths.

9.5 MEASUREMENT OF DELTA-AMINOLEVULINIC ACID DEHYDRASE ACTIVITY

Delta-aminolevulinic acid dehydrase (5-aminolevulinate hydrolase; porphobilinogen synthetase; E.C. 4.2.1.24; ALA-D) is an allosteric sulfhydryl enzyme that mediates the conversion of two units of δ-aminolevulinic acid to porphobilinogen, a precursor in the heme biosynthetic pathway to the porphyrins. Lead's inhibition of the activity of this enzyme is the enzymological basis of ALA-D's diagnostic utility in assessing lead exposure using erythrocytes.

A number of sampling precautions are necessary when measuring this enzyme's activity. ALA-D activity is modified by the presence of zinc as well as by lead. Consequently, blood collection tubes that have high background zinc content, mainly in the rubber stoppers, must be avoided completely or care taken to avoid stopper contact with blood. Nackowski et al. (1977) observed that the presence of zinc in blood collection tubes is a pervasive problem, and it appears that plastic-cup tubes are the only practical means to avoid it. To guard against zinc in the tube itself, it would appear prudent to determine the extent of zinc leachability by blood and to use one tube lot, if possible. Heparin is the anticoagulant of choice, as the lead binding agent, EDTA, or other chelants would affect the lead-enzyme interaction. The relative stability of the enzyme in blood makes rapid determinations of activity necessary, preferably as soon after collection as possible. Even with refrigeration, analysis of activity should be done within 24 hours (Berlin and Schaller, 1974). Furthermore, porphobilinogen is light-labile, which requires that the assay be done under restricted light.

Various procedures for ALA-D activity measurement are chemically based on measurement of porphobilinogen generated from the substrate, δ-ALA porphobilinogen is condensed with p-dimethylaminobenzaldehyde (Ehrlich's reagent) to yield a chromophore measured at 553 nm in a spectrophotometer. In the European Standardized Method for ALA-D activity measurement (Berlin and Schaller, 1974), developed with the collaboration of nine laboratories for use with blood samples having relatively low lead content, triplicate blood samples (0.2 ml) are hemolyzed, along with a blood blank, with water for 10 minutes at 37°C. Samples are then mixed with δ-ALA solution followed by a 60-minute incubation. The enzyme reaction is terminated by addition of a solution of mercury (II) in trichloroacetic acid, followed by centrifugation and filtration. Filtrates are mixed with modified Ehrlich's reagent (p-dimethylaminobenzalehyde in trichloroacetic/perchloric acid mixture) and allowed to react for 5 minutes, followed by chromophore measurement in a spectrophotometer at 555 nm. Activity is quantified in terms of μM δ-ALA/min-l erythrocytes. It should be noted that the amount of phosphate for Solution A in Berlin & Schaller's report should be 1.78 g, not the 1.38 g stated. In a micro scale variation, Granick et al. (1973) used only 5 μl of blood and terminated the assay by trichloroacetic acid.

In comparing various reports concerning the relationship between lead exposure and ALA-D inhibition, attention should be paid to the units of activity measurement employed with the different techniques. Berlin and Schaller's (1974) procedure expresses activity as μM ALA/min/l cells, while Tomokuni's (1974) method expresses activity as μM porphobilinogen/hr/ml cells. Similarly, when comparing the Bonsignore et al. (1965) procedure to that of Berlin and Schaller (1974), a conversion factor of 3.8 is necessary when converting from Bonsignore to European Standard Method units (Trevisan et al., 1981).

Several factors have been shown to affect ALA-D activity. Rather than measuring enzyme activity in blood once, Granick et al. (1973) measured activity before and after treatment with dithiothreitol, an agent that reactivates the enzyme by complexing lead. The ratio of activated to unactivated enzymes vs. blood lead levels accommodates inherent differences in enzyme activity among individuals due to genetic factors and other reasons. Other agents for such activation include zinc (Finelli et al., 1975) and zinc plus glutathione (Mitchell et al., 1977). In the Mitchell et al. (1977) study, non-physiological levels of zinc were used. Wigfield and Farant (1979) found that enzyme activity is related to assay pH; thus, reduced activity from such a pH-activity relationship could be misinterpreted as lead inhibition. These researchers find that pH shifts away from optimal, in terms of activity, as blood lead content increases and the incubation step proceeds.

9.6 MEASUREMENT OF DELTA-AMINOLEVULINIC ACID IN URINE AND OTHER MEDIA

Delta-aminolevulinic acid (δ-ALA) levels increase with elevated lead exposure, due to the inhibitory effect of lead on the activity of ALA dehydrase and/or the increase of ALA synthetase activity by feedback derepression. The result is that this intermediate in heme biosynthesis rises in the body and eventually results in increased urinary excretion. The measurement of this metabolite in urine provides an indication of the level of lead exposure.

The ALA content of urine samples is stable for approximately 2 weeks or more if urine samples are acidified with tartaric or acetic acid and kept refrigerated. Values of ALA-U are adjusted for urine density, if concentration is expressed in mg/l or is measured per gram creatinine. As noted in the case of urinary lead measurement, 24-hour collection is more desirable than spot sampling.

Five manual and one automated procedure for urinary ALA measurement are most widely used. Mauzerall and Granick (1956) and Davis and Andelman (1967) described the most involved procedures, requiring the initial chromatographic separation of ALA. The approach of Grabecki et al. (1967) omitted chromatographic isolation, whereas the automated variation of Lauwerys et al. (1972) omitted prechromatography but included the use of an internal standard. Tomokuni and Ogata (1972) omitted, chromatography but employed solvent extraction to isolate the pyrrole intermediate.

Mauzerall and Granick (1956) condensed ALA with a β-dicarbonyl compound, acetylacetone, at pH 4.6 to yield a pyrrole intermediate (Knorr condensation reaction), which was further reacted with p-dimethylaminobenzaldehyde in perchloric/acetic acid. The samples were then read in a spectrophotometer at 553 nm 15 minutes after mixing. In this method, there is separation of both porphobilinogen and ALA from urine by means of a dual column configuration of cation and anion exchange resins. The latter retains the porphobilinogen and the former separates ALA from urea. The detection limit is 3 μmoles/l urine. In the modification of this method by Davis and Andelman (1967), disposable cation/anion resin cartridges were used, in a sequential configuration, to expedite chromatographic separation and increase sample analysis rate. Commercial (Bio-Rad) disposable columns based on this design are now available and appear satisfactory.

In these two approaches (Mauzerall and Granick, 1956; Davis and Andelman, 1967), the problem of interference due to aminoacetone, a metabolite occurring in urine, is not taken into account. However, Marver et al. (1966) used Dowex-1 in a chromatographic step subsequent to the condensation reaction to form the pyrrole. This separates the ALA derivative from that of the aminoacetone. Similarly, Schlenker et al. (1964) used an IRC column to retain aminoacetone.

Tomokuni and Ogata (1972) condensed ALA with ethylacetoacetate and extracted the resulting pyrrole with ethyl acetate. The extract was then treated with Ehrlich's reagent and the resulting chromophore measured spectrophotometrically. Lauwerys et al. (1972) developed an automated ALA analysis method for lead worker screening, in which ALA was added in known amount as an internal standard and the pre-chromatography avoided. They reported a high correlation ($r = 0.98$, no range available) with the procedure of Mauzerall and Granick (1956).

Roels et al. (1974) compared the relative proficiency of four methods -- those of Mauzerall and Granick (1956), Davis and Andelman (1967), the Lauwerys et al. (1972) automated version, and the Grabecki et al. (1967) method, which omits chromatographic separation and is normally used with occupational screening. The chromatographic methods gave identical results over the range of 0-60 mg ALA/l urine, while the automated method showed a positive bias at <6 mg/l. The Grabecki et al. (1967) technique was the least satisfactory of the procedures compared. Roels et al. (1974) also noted that commercial ion-exchange columns resulted in low variability (<10 percent).

Della-Fiorentina et al. (1979) combined the Tomokuni and Ogata (1972) extraction method with a correction equation for urine density. Up to 25 mg ALA/l, the C.V. was ≤4 percent along with a good correlation ($r = 0.937$) with the Davis and Andelman (1967) technique. While there is a time saving in avoiding prechromatography, it is necessary to prepare a curve relating urine density to a correction factor for quantitative measurement.

Although ALA analysis is normally done with urine as the indicator medium, Haeger-Aronsen (1960) reported a similar colorimetric method for blood and MacGee et al. (1977) described a gas-liquid chromatographic method for ALA in plasma as well as urine. Levels of ALA in plasma are much lower than those in urine. In the latter method, ALA was isolated from plasma, reacted with acetyl-acetone, and partitioned into a solvent (trimethylphenylhydroxide), which also served for pyrolytic methylation in the injection port of the gas-liquid chromatograph, the methylated pyrrole being more amenable to chromatographic isolation than the more polar precursor. For quantification, an internal standard, 6-amino-5-oxohexanoic acid, was used. The sample requirement is 3 ml plasma. Measured levels ranged from 6.3 to 73.5 ng ALA/ml plasma, and yielded values that were approximately 10-fold lower than the colorimetric techniques (O'Flaherty et al., 1980).

9.7 MEASUREMENT OF PYRIMIDINE-5'-NUCLEOTIDASE ACTIVITY

Erythrocyte pyrimidine-5'-nucleotidase (5'-ribonucleotide phosphohydrolase, E.C. 3.1.3.5, Py5N) catalyzes the hydrolytic dephosphorylation of the pyrimidine nucleotides uridine monophosphate (UMP) and cytidinemonophosphate (CMP) to uridine and cytidine (Paglia and Valentine, 1975). Enzyme inhibition by lead in humans and animals results in incomplete degradation of

reticulocyte RNA fragments, accumulation of the nucleotides, and increased cell hemolysis (Paglia et al., 1975; Paglia and Valentine, 1975; Angle and McIntire, 1978; George and Duncan, 1982).

There are two methods for measurement of Py5N activity. One is quite laborious in terms of time and manipulation, while the other is shorter but requires the use of radioisotopes and radiometric measurement. In Paglia and Valentine's (1975) method, heparinized venous blood was filtered through cotton or a commercial cellulose preparation to separate erythrocytes from platelets and leukocytes. Cells were given multiple saline washings, packed lightly, and subjected to freeze hemolysis. The hemolysates were dialyzed against a saline-Tris buffer containing $MgCl_2$ and EDTA to remove nucleotides and other phosphates. The assay system consists of dialyzed hemolysate, $MgCl_2$, Tris buffer at pH 8.0, and either UMP or CMP; incubation is for 2 hours at 37°C. Activity is terminated by treatment with 20 percent trichloroacetic acid, followed by centrifugation. The supernatant inorganic phosphate, P_i, is measured by the classic method of Fiske and Subbarow (1925), the phosphomolybdic acid complex being measured spectrophotometrically at 660 nm. A unit of enzyme activity is expressed as μmol P_i/hr/g hemoglobin. Hemolysates appear to be stable (90 percent) with refrigeration at 4°C for up to 6 days, provided that mercaptoethanol is added at the time of assay. Like the other method, activity measurement requires the determination of hemoglobin.

In the simpler approach of Torrance et al. (1977), which can be feasibly applied to much larger numbers of samples, erythrocytes were separated from leukocytes and platelets with a 1:1 mixture of microcrystalline and alphacellulose, followed by saline washing and hemolysis with a solution of mercaptoethanol and EDTA. Hemolysates were incubated with a medium containing purified ^{14}C-CMP and $MgCl_2$ for 30 minutes at 37°C. The reaction was terminated by sequential addition of barium hydroxide and zinc sulfate solution. Proteins and unreacted nucleotide were precipitated, leaving the labeled cytidine in the supernatant. Aliquots were measured for ^{14}C activity in a liquid scintillation counter. Enzyme activity was expressed as nM CMP/min/g hemoglobin. The blank activity was determined for each sample by carrying out the precipitation step as soon as the hemolysate was mixed with the labeled CMP, i.e., t = 0. This procedure shows a good correlation (r = 0.94; range: 135-189 enzyme units) with the method of Paglia and Valentine (1975). The two methods express units of enzyme activity differently, so that one must know which method is used when comparing enzyme activity.

9.8 SUMMARY

The sine qua non of a complete understanding of a toxic agent's effects on an organism, e.g., dose-effect relationships, is quantitative measurement of either that agent in some biological medium or a physiological parameter associated with exposure to the agent. Quantitative analysis involves a number of discrete steps, all of which contribute to the overall reliability of the final analytical result: sample collection and shipment, laboratory handling, instrumental analysis, and criteria for internal and external quality control.

From a historical perspective, it is clear that the definition of "satisfactory analytical method" for lead has been steadily changing as new and more sophisticated equipment becomes available and understanding of the hazards of pervasive contamination along the analytical course increases. The best example of this is the use of the definitive method for lead analysis, isotope-dilution mass spectrometry in tandem with "ultra-clean" facilities and sampling methods, to demonstrate conclusively not only the true extent of anthropogenic input of lead to the environment over the years but also the relative limitations of most of the methods for lead measurement used today.

9.8.1 Determinations of Lead in Biological Media

The low levels of lead in biological media, even in the face of excessive exposure, and the fact that sampling of such media must be done against a backdrop of pervasive lead contamination necessitates that samples be carefully collected and handled. Blood lead sampling is best done by venous puncture and collection into low-lead tubes after careful cleaning of the puncture site. The use of finger puncture as an alternative method of sampling should be avoided, if feasible, given the risk of contamination associated with the practice in industrialized areas. While collection of blood onto filter paper enjoyed some popularity in the past, paper deposition of blood requires special correction for hematrocrit/hemoglobin level.

Urine sample collection requires the use of lead-free containers as well as addition of a bacteriocide. If feasible, 24-hour sampling is preferred to spot collection. Deciduous teeth vary in lead content both within and across type of dentition. Thus a specific tooth type should be uniformly obtained for all study subjects and, if possible, more than a single sample should be obtained from each subject.

Measurements of Lead in Blood. Many reports over the years have purported to offer satisfactory analysis of lead in blood and other biological media, often with severe inherent limitations on accuracy and precision, meager adherence to criteria for accuracy and precision, and a limited utility across a spectrum of analytical applications. Therefore, it is only useful to discuss "definitive" and, comparatively speaking, "reference" methods presently used.

In the case of lead in biological media, the definitive method is isotope-dilution mass spectrometry (IDMS). The accuracy and unique precision of IDMS arise from the fact that all manipulations are on a weight basis involving simple procedures, and measurements entail only lead isotope ratios and not the absolute determinations of the isotopes involved, greatly reducing instrumental corrections and errors. Reproducible results to a precision of one part in 10^4-10^5 are routine with appropriately designed and competently operated instrumentation. Although this methodology is still not recognized in many laboratories, it was the first breakthrough, in tandem with "ultra-clean" procedures and facilities, to definitive methods for indexing the progressive increase in lead contamination of the environment over the centuries. Given the expense, required level of operator expertise, and time and effort involved for measurements by IDMS, this methodology mainly serves for analyses that either require extreme accuracy and precision, e.g., geochronometry, or for the establishment of analytical reference material for general testing purposes or the validation of other methodologies.

While the term "reference method" for lead in biological media cannot be rigorously applied to any procedures in popular use, the technique of atomic absorption spectrometry in its various configurations or the electrochemical method, anodic stripping voltammetry, come closest to meriting the designation. Other methods that are generally applied in metal analyses are either limited in sensitivity or are not feasible for use on theoretical grounds for lead analysis.

Atomic absorption spectrometry (AAS) as applied to analysis of whole blood generally involves flame or flameless micromethods. One macromethod, the Hessel procedure, still enjoys some popularity. Flame microanalysis, the Delves cup procedure, applied to blood lead appears to have an operational sensitivity of about 10 µg Pb/dl blood and a relative precision of approximately 5 percent in the range of blood lead seen in populations in industrialized areas. The flameless, or electrothermal, method of AAS enhances sensitivity about 10-fold, but precision can be more problematical because of chemical and spectral interferences.

The most widely used and sensitive electrochemical method for lead in blood is anodic stripping voltammetry (ASV). For most accurate results, chemical wet ashing of samples must be carried out, although this process is time-consuming and requires the use of lead-free reagents. The use of metal exchange reagents has been employed in lieu of the ashing step to liberate lead from binding sites, although this substitution is associated with less precision. For the ashing method, relative precision is approximately 5 percent. In terms of accuracy and sensitivity, it appears that there are problems at low levels, e.g., 5 µg/dl or below, particularly if samples contain elevated cooper levels.

Lead in Plasma. Since lead in whole blood is virtually all confined to the erythrocyte, plasma levels are quite low and it appears that extreme care must be employed to reliably measure plasma levels. The best method for such measurement is IDMS, in tandem with ultra-clean facility use. Atomic absorption spectrometry is satisfactory for comparative analyses across a range of relatively high whole blood values.

Lead in Teeth. Lead measurement in teeth has involved either whole tooth sampling or analysis of specific regions, such as primary or circumpulpal dentine. In either case, samples must be solublized after careful surface cleaning to remove contamination; solubilization is usually accompanied by either wet ashing directly or ashing subsequent to a dry ashing step.

Atomic absorption spectrometry and anodic stripping have been employed more frequently for such determinations than any other method. With AAS, the high mineral content of teeth argues for preliminary isolation of lead via chelation-extraction. The relative precision of analysis for within-run measurement is around 5-7 percent, with the main determinant of variance in regional assay being the initial isolation step. One change from the usual methods for such measurement is the in situ measurement of lead by X-ray fluorescence spectrometry in children. Lead measured in this fashion allows observation of on-going lead accumulation, rather than waiting for exfoliation.

Lead in Hair. Hair as an exposure indicator for lead offers the advantages of being non-invasive and a medium of indefinite stability. However, there is still the crucial problem of external surface contamination, which is such that it is still not possible to state that any cleaning protocol reliably differentiates between external and internally deposited lead.

Studies that demonstrate a correlation between increasing hair lead and increasing severity of a measured effect probably support arguments for hair being an external indicator of exposure. It is probably also the case, then, that such measurement, using cleaning protocols that have not been independently validated, will overstate the relative accumulation of "internal" hair lead in terms of some endpoint and will also underestimate the relative sensitivity of changes in internal lead content with exposure. One consequence of this would be, for example, an apparent threshold for a given effect in terms of hair lead which is significantly above the actual threshold. Because of these concerns, hair is best used with the simultaneous measurement of blood lead.

Lead in Urine. Analysis of lead in urine is complicated by the relatively low levels of the element in this medium as well as the complex mixture of mineral elements present. Urine lead levels are most useful and also somewhat easier to determine in cases of chelation mobilization or chelation therapy, where levels are high enough to permit good precision and dilution of matrix interference.

Samples are probably best analyzed by prior chemical wet ashing, using the usual mixture of acids. Both anodic stripping voltammetry and atomic absorption spectrometry have been applied to urine analysis, with the latter more routinely used and usually with a chelation/extraction step.

Lead in Other Tissues. Bone samples require cleaning procedures for removal of muscle and connective tissue and chemical solubilization prior to analysis. Methods of analysis are comparatively limited and it appears that flameless atomic absorption spectrometry is the technique of choice.

Lead measurements in bone, in vivo, have been reported with lead workers, using X-ray fluorescence analysis and a radioisotopic source for excitation. One problem with this approach with moderate lead exposure is the detection limit, approximately 20 ppm. Soft organ analysis poses a problem in terms of heterogeneity in lead distribution within an organ (e.g., brain and kidney. In such cases, regional sampling or homogenization must be carried out. Both flame and flameless atomic absorption spectrometry appear to be satisfactory for soft tissue analysis and are the most widely used.

Quality Assurance Procedures in Lead Analyses. In terms of available information, the major focus in establishing quality control protocols for lead has involved whole blood measurements. Translated into practice, quality control revolves around steps employed within the laboratory, using a variety of internal checks, and the further reliance on external checks, such as a formal continuing multi-laboratory proficiency testing program.

Within the laboratory, quality assurance protocols can be divided into start-up and routine procedures, the former involving establishment of detection limits, within-run and between-run precision, analytical recovery, and comparison with some reference technique within or outside the laboratory. The reference method is assumed to be accurate for the particular level of lead in some matrix at a particular point in time. Correlation with such a method at a satisfactory level, however, may simply indicate that both methods are equally inaccurate but performing with the same level of precision proficiency. More preferable is the use of certified samples having lead at a level established by the definitive method.

For blood lead, the Centers for Disease Control periodically survey overall accuracy and precision of methods used by reporting laboratories. In terms of overall accuracy and precision, one such survey found that anodic stripping voltammetry as well as the Delves cup and extraction variations of atomic absorption spectrometry performed better than other procedures. These results do not mean that a given laboratory cannot perform better with a particular technique; rather, such data are of assistance for new facilities choosing among methods.

Of particular value to laboratories carrying out blood lead analysis are the external quality assurance programs at both the state and federal levels. The most comprehensive

proficiency testing program is that carried out by the Centers for Disease Control, USPHS. This program actually consists of two subprograms, one directed at facilities involved in lead poisoning prevention and screening (Center for Environmental Health) and the other concerned with laboratories seeking certification under the Clinical Laboratories Improvement Act of 1967 as well as under regulations of the Occupational Safety and Health Administration's (OSHA) Laboratory Improvement Program Office. Overall, the proficiency testing programs have served their purpose well, judging from the relative overall improvements in reporting laboratories over the years of the programs' existence. In this regard, OSHA criteria for laboratory certification require 8 of 9 samples be correctly analyzed for the previous quarter. This level of required proficiency reflects the ability of a number of laboratories to actually perform at this level.

9.8.2 Determination of Erythrocyte Porphyrin (Free Erythrocyte Protoporphyrin, Zinc Protoporphyrin)

With lead exposure, there is an accumulation of erythrocyte protoporphyrin IX, owing to impaired placement of divalent iron to form heme. Divalent zinc occupies the place of the native iron. Depending upon the method of analysis, either metal-free erythrocyte porphyrin or zinc protoporphyrin (ZPP) is measured, the former arising from loss of zinc in the chemical manipulation. Virtually all methods now in use for EP analysis exploit the ability of the porphyrin to undergo intense fluorescence when excited by ultraviolet light. Such fluorometric methods can be further classified as wet chemical micromethods or direct measuring fluorometry using the hematofluorometer. Owing to the high sensitivity of such measurement, relatively small blood samples are required, with liquid samples or blood collected on filter paper.

The most common laboratory or wet chemical procedures now in use represent variations of several common chemical procedures: 1) treatment of blood samples with a mixture of ethyl acetate/acetic acid followed by a repartitioning into an inorganic acid medium, or 2) solubilization of a blood sample directly into a detergent/buffer solution at a high dilution. Quantification has been done using protoporphyrin, coproporphyrin, or zinc protoporphyrin IX plus pure zinc ion. The levels of precision for these laboratory techniques vary somewhat with the specifics of analysis. The Piomelli method has a coefficient of variation of 5 percent, while the direct ZPP method using buffered detergent solution is higher and more variable.

The recent development of the hematofluorometer has made it possible to carry out EP measurements in high numbers, thereby making population screening feasible. Absolute calibration is necessary and requires periodic adjustment of the system using known concentrations of

EP in reference blood samples. Since these units are designed for oxygenated blood, i.e., capillary blood, use of venous blood requires an oxygenation step, usually a moderate shaking for several minutes. Measurement of low or moderate levels of EP can be affected by interference with bilirubin. Competently employed, the hematofluorometer appears to be reasonably precise, showing a total coefficient of variation of 4.11-11.5 percent. While the comparative accuracy of the unit has been reported to be good relative to the reference wet chemical technique, a very recent study has shown that commercial units carry with them a significant negative bias, which may lead to false negatives in subjects having only moderate EP elevation. Such a bias in accuracy has been difficult to detect in existing EP proficiency testing programs. It appears that, by comparision to wet methods, the hematofluorometer should be restricted to field use rather than becoming a substitute in the laboratory for chemical measurement, and field use should involve periodic split-sample comparison testing with the wet method.

9.8.3 Measurement of Urinary Coproporphyrin

Although EP measurement has largely supplanted the use of urinary coproporphyrin analysis (CP-U) to monitor excessive lead exposure in humans, this measurement is still of value in that it reflects active intoxication. The standard analysis is a fluorometric technique, whereby urine samples are treated with buffer, and an oxidant (iodine) is added to generate CP from its precursor. The CP-U is then partitioned into ethyl acetate and re-extracted with dilute hydrochloric acid. The working curve is linear below 5 µg CP/dl urine.

9.8.4 Measurement of Delta-Aminolevulinic Acid Dehydrase Activity

Inhibition of the activity of the erythrocyte enzyme, delta-aminolevulinic acid dehydratase (ALA-D), by lead is the basis for using such activity in screening for excessive lead exposure. A number of sampling and sample handling precautions attend such analysis. Since zinc (II) ion will offset the degree of activity inhibition by lead, blood collecting tubes must have extremely low zinc content. This essentially rules out the use of rubber-stoppered blood tubes. Enzyme stability is such that the activity measurement is best carried out within 24 hours of blood collection. Porphobilinogen, the product of enzyme action, is light-labile and requires the assay be done in restricted light. Various procedures for ALA-D measurement are based on measurement of the level of the chromophoric pyrrole (approximately 555 nm) formed by condensation of the porphobilinogen with p-dimethylaminobenzaldehyde.

In the European Standardized Method for ALA-D activity determination, blood samples are hemolyzed with water, ALA solution added, followed by incubation at 37°C, and the reaction terminated by a solution of mercury (II) in trichloroacetic acid. Filtrates are treated with

modified Ehrlich's reagent (p-dimethylaminobenzaldehyde) in trichloroacetic/perchloroacetic acid mixture. Activity is quantified in terms of micromoles ALA/min/liter erythrocytes.

One variation in the above procedure is the initial use of a thiol agent, such as dithiothreotol, to reactivate the enzyme, giving a measure of the full native activity of the enzyme. The ratio of activated/unactivated activity vs. blood lead levels accomodates genetic differences between individuals.

9.8.5 Measurement of Delta-Aminolevulinic Acid in Urine and Other Media

Levels of delta-aminolevulinic acid (δ-ALA) in urine and plasma increase with elevated lead exposure. Thus, measurement of this metabolite, generally in urine, provides an index of the level of lead exposure. ALA content of urine samples (ALA-U) is stable for about two weeks or more with sample acidification and refrigeration. Levels of ALA-U are adjusted for urine density or expressed per unit creatinine. If feasible, 24-hour collection is more desirable than spot sampling.

Virtually all the various procedures for ALA-U measurement employ preliminary isolation of ALA from the balance of urine constituents. In one method, further separation of ALA from the metabolite aminoacetone is done. Aminoacetone can interfere with colorimetric measurement. ALA is recovered, condensed with a beta-dicarbonyl compound, e.g., acetyl acetone, to yield a pyrrole intermediate. This intermediate is then reacted with p-dimethylaminobenzaldehyde in perchloric/acetic acid, followed by colorimetric reading at 553 nm. In one variation of the basic methodology, ALA is condensed with ethyl acetoacetate directly and the resulting pyrrole extracted with ethyl acetate. Ehrlich's reagent is then added as in other procedures and the resulting chromophore measured spectrophotometrically.

Measurement of ALA in plasma is much more difficult than in urine, since plasma ALA is at nanogram/milliter levels. In one gas-liquid chromatographic procedure, ALA is isolated from plasma, reacted with acetyl acetone and partitioned into a solvent that also serves for pyrolytic methylation of the involatile pyrrole in the injector port of the chromatograph, making the derivative more volatile. For quantification, an interval standard, 6-amino-5-oxohexanoic acid, is used. While the method is more involved, it is more specific than the older colorimetric technique.

9.8.6 Measurement of Pyrimidine-5'-Nucleotidase Activity

Erythrocyte pyrimidine-5'-nucleotidase (Py5N) activity is inhibited with lead exposure. Presently two different methods are used for assaying the activity of this enzyme. The older method is quite laborious in time and effort, whereas the more recent approach is shorter but uses radioisotopes and radiometric measurement.

In the older method, heparinized venous blood is filtered through cellulose to separate erythrocytes from platelets and leukocytes. Cells are then freeze-fractured and the hemolysates dialyzed to remove nucleotides and other phosphates. This dialysate is then incubated in the presence of a nucleoside monophosphate and cofactors, the enzyme reaction being terminated by treatment with trichloroacetic acid. The inorganic phosphate isolated from added substrate is measured colorimetrically as the phosphomolybdic acid complex.

In the radiometric assay, hemolysates obtained as before are incubated with pure ^{14}C-CMP. By addition of a barium hydroxide/zinc sulfate solution, proteins and unreacted nucleotide are precipitated, leaving labeled cytidine in the supernatant. Aliquots are measured for ^{14}C activity in a liquid scintillation counter. This method shows a good correlation with the earlier technique.

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10. METABOLISM OF LEAD

10.1 INTRODUCTION

The absorption, distribution, retention, and excretion of lead in humans and animals as well as the various factors that mediate the extent of toxicokinetic processes are discussed in this chapter. While inorganic lead is the form of the element that has been most heavily studied, organolead compounds are also emitted into the environment and, as they are quite toxic, they are also included in the discussion. Since the preparation of the 1977 Air Quality Criteria Document for Lead (U.S. Environmental Protection Agency, 1977), a number of reports have appeared that have proved particularly helpful in both quantifying the various processes to be discussed in this chapter and assessing the interactive impact of factors such as nutritional status in determining internal exposure risk.

10.2 LEAD ABSORPTION IN HUMANS AND ANIMALS

The amounts of lead entering the bloodstream from various routes of absorption are determined not only by the levels of the element in the particular media, but also by the various physical and chemical parameters that characterize lead. Furthermore, specific host factors, such as age and nutritional status, are important, as is interindividual variability. Additionally, in order to assess absorption rates, it is necessary to know whether or not the subject is in "equilibrium" with respect to a given level of lead exposure.

10.2.1 Respiratory Absorption of Lead

The movement of lead from ambient air to the bloodstream is a two-part process: a fraction of air lead is deposited in the respiratory tract and, of this deposited amount, some fraction is subsequently absorbed directly into the bloodstream or otherwise cleared from the respiratory tract. At present, enough data exist to make some quantitative statements about both of these components of respiratory absorption of lead.

The 1977 Air Quality Criteria Document for Lead described the model of the International Radiological Protection Commission (IRPC) for the deposition and removal of lead from the lungs and the upper respiratory tract (International Radiological Protection Commission, 1966). Briefly, the model predicts that 35 percent of lead inhaled from ambient air is deposited in the airways, with most of this going to the lung. The IRPC model predicts a total deposition of 40-50 percent for particles with an aerodynamic diameter of 0.5 μm and indicates that the absorption rate would vary, depending on the solubility of the particular form.

10.2.1.1 Human Studies. Table 10-1 tabulates the various studies of human subjects that provide data on the deposition of inorganic lead in the respiratory tract. Studies of this type have involved diverse methodology to characterize the inhaled particles in terms of both size (and size ranges) and fractional distribution. The use of radioisotopic or stable lead isotopes to directly or indirectly measure lead deposition and uptake into the bloodstream has been particularly helpful in quantifying these processes.

From the studies of Kehoe (1961a,b,c) and their update by Gross (1981) as well as data from Chamberlain et al. (1978), Morrow et al. (1980), and Nozaki (1966), it appears that the respiratory deposition of airborne lead as encountered in the general population is approximately 30-50 percent, depending on particle size and ventilation rates. Ventilation rate is particularly important with submicron particles, where Brownian diffusion governs deposition, since a slower breathing rate enhances the frequency of collisions of particles with the alveolar wall.

Figure 10-1 reproduces a composite figure of Chamberlain et al. (1978) that compares data, both calculated and experimentally measured, on the relationship of percentage deposition to particle size. With increasing particle size, deposition rate decreases to a minimum over the range where Brownian diffusion predominates, followed by an increase in deposition with size (>0.5 μm MMAD) as impaction and sedimentation become the main deposition factors.

In contrast to the ambient air or chamber data tabulated in Table 10-1, higher deposition rates in some occupational settings are associated with relatively large particles. However, much of this deposition will be in the upper respiratory tract, with eventual movement to the gastrointestinal tract by ciliary action and swallowing. Mehani et al. (1966) measured deposition rates in battery workers and workers in marine scrap yards and observed total depositon rates of 28-70 percent. Chamberlain and Heard (1981) calculated an absorption rate for particle sizes encountered in workplace air of appproximately 47 percent.

Systemic absorption of lead from the lower respiratory tract occurs directly, while much of the absorption from the upper tract involves swallowing and some uptake in the gut. From the radioactive isotope data of Chamberlain et al. (1978) and Morrow et al. (1980), and the stable isotope studies of Rabinowitz et al. (1977), it can be concluded that lead deposited in the lower respiratory tract is quantitatively absorbed.

Chamberlain et al. (1978) used ^{203}Pb-labeled lead in engine exhaust, lead oxide, or lead nitrate aerosols in experiments where human subjects inhaled the lead from a chamber through a mouthpiece or in wind tunnel aerosols. By 14 days, approximately 90 percent of the label was removed from the lung. Lead movement into the bloodstream could not be described by a simple exponential function; 20 percent was absorbed within 1 hour and 70 percent within 10 hours.

TABLE 10-1. DEPOSITION OF LEAD IN THE HUMAN RESPIRATORY TRACT

Form	Particle size	Exposure	Percent deposition	Reference
Pb_2O_3 aerosols from engine exhaust	0.05 μm median count diameter in 38 studies; 5 subjects exposed to average of 0.9 μm	Chamber studies; 10, 20, or 150 μg/m^3; 3 hr on alternate days; 12 subjects	30-70% (mean: 48%) for mainly 0.05 μm particles	Kehoe, 1961a,b,c; Gross, 1981
Lead "fumes" made in induction furnace	0.05-1.0 μm mean diameter	Mouthpiece/aerosol chamber; 10 mg/m^3; adult subjects	42% 0.05 μm; 63% 1.0 μm	Nozaki, 1966
^{203}Pb-labeled Pb_2O_3 aerosol	Mean densities of 0.02, 0.04, 0.09 μm	Mouthpiece/aerosol chamber; adult subjects	80% 0.02 μm; 45% 0.04 μm; 30% 0.09 μm	Chamberlain et al., 1978
Ambient air lead near motorway and other urban areas in U.K.	Mainly 0.1 μm	2-10 μg/m^3; adult subjects	60%, fresh exhaust; 50% other urban area	Chamberlain et al., 1978
^{203}Pb-labeled $Pb(OH)_2$ or $PbCl_2$ aerosols	Both forms at 0.25 μm MMAD	50 liters air; 0.2 μCi/liter; adult subjects	23%, chloride; 26%, hydroxide	Morrow et al., 1980
Lead in workplace air; battery factory and shipbreaking operations	Not determined; defined as fumes, fine dust, or coarse dust	3 adult groups: 23 μg/m^3 - controls 86 μg/m^3 - battery workers 180 μg/m^3 - scrap yard	47%, battery workers; 39%, shipyard and controls	Mehani, 1966

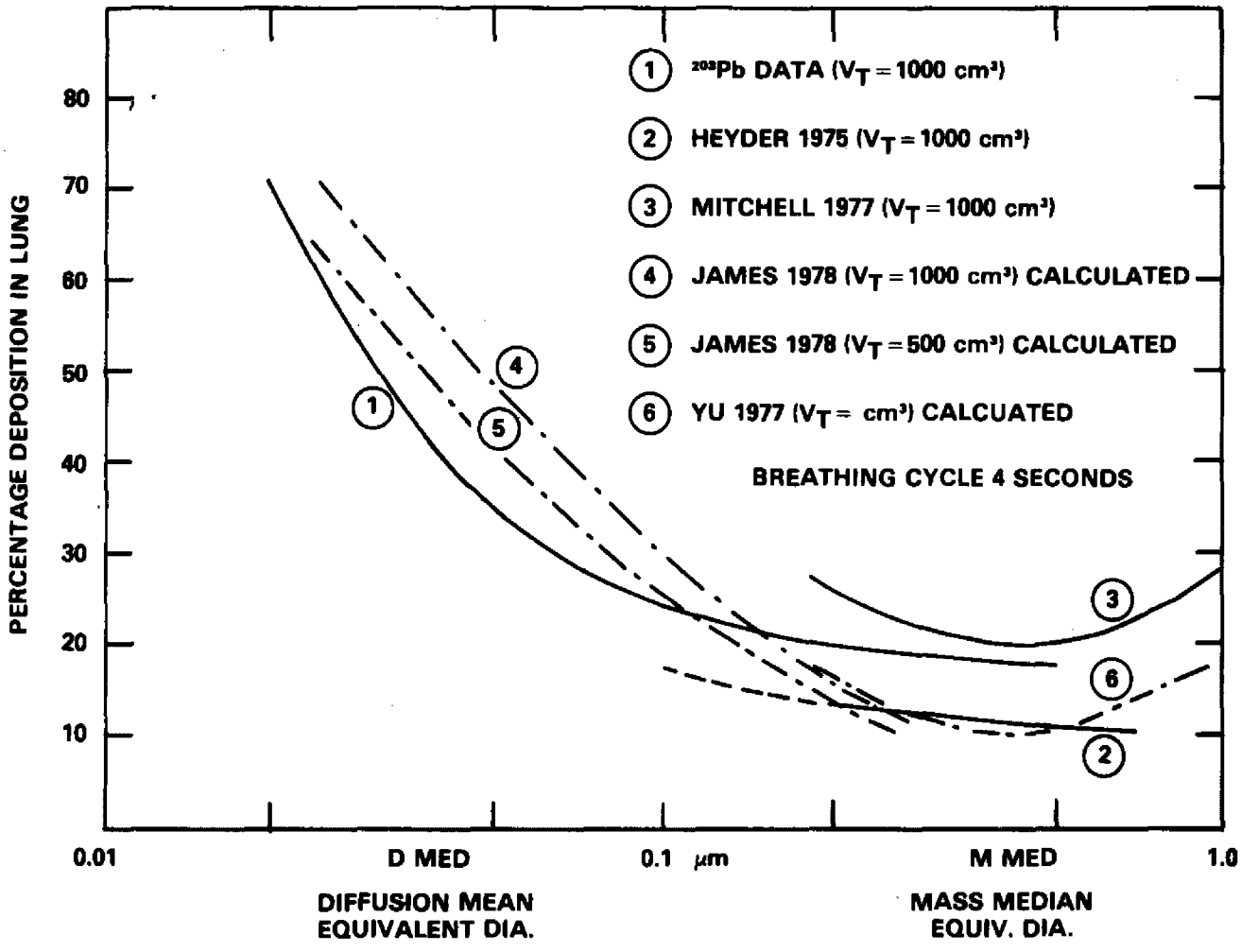

Figure 10-1. Effect of particle size on lead deposition rate in the lung.

Source: Chamberlain et al. (1978).

Rabinowitz et al. (1977) administered ^{204}Pb tracer to young adult volunteers and were able to determine by isotope tracer as well as balance data that 14 μg of lead was absorbed by these subjects daily at ambient air lead levels of 1-2 $\mu g/m^3$. Assuming a daily ventilation rate of 20 m^3 a deposition rate of 50 percent of ambient air (Chamberlain et al., 1978), and a mean air lead level of 1.5 $\mu g/m^3$ (2.0 $\mu g/m^3$ outside the study unit, 1.0 $\mu g/m^3$ inside, as determined by the authors), then 15 μg lead was available for absorption. Hence, better than 90 percent of deposited lead was absorbed daily.

Morrow et al. (1980) followed the systemic uptake of ^{203}Pb-labeled lead in 17 adult subjects using either lead chloride or lead hydroxide aerosols with an average size of 0.25 (±0.1) μm MMAD. Half of the deposited fraction of either aerosol was absorbed in 14 hours or less. The radiolabel data described above are consistent with the results of Hursh and Mercer (1970), who studied the systemic uptake of ^{212}Pb on a carrier aerosol.

Given the apparent invariance of absorption rate for deposited lead in the above studies as a function of chemical form of the element (Chamberlain et al., 1978; Morrow et al., 1980), it seems that inhaled lead lodging deep in the respiratory tract is absorbed equally, regardless of form. Supporting evidence for total human systemic uptake of lead comes from autopsy tissue analysis for lead content. Barry (1975) found that lead was not accumulated in the lungs of lead workers. This may also be seen in the data of Gross et al. (1975) for non-occupationally exposed subjects.

All of the available data for lead deposition and uptake from the respiratory tract in humans have been obtained with adults, and quantitative comparisons with the same exposures in children are not possible. Although children 2 years of age weigh one-sixth as much as an adult, they inhale 40 percent as much air lead as adults (Barltrop, 1972). James (1978) has also taken into account differences in airway dimensions in adults vs. children, and has estimated that, often controlling for weight, the 10-year-old child has a deposition rate 1.6- to 2.7-fold higher than the adult.

10.2.1.2 Animal Studies. Experimental animal data for quantitative assessment of lead deposition and absorption for the lung and upper respiratory tract are limited. The available information does, however, support the finding that respired lead is extensively and rapidly absorbed.

Morgan and Holmes (1978) exposed adult rats, by nose-only technique, to a ^{203}Pb-labeled engine exhaust aerosol generated in the same manner as by Chamberlain et al. (1978) over a period of 8 days. Exposure was at a level of 21.9-23.6 nCi label/liter chamber air. Adjusting for deposition on the animal pelt, 20-25 percent of the label was deposited in the lungs. Deposited lead was extensively taken up in blood: 50 percent within 1 hour and, 98 percent within 7 days. The absorption rate kinetic profile was similar to that reported for humans (Chamberlain et al., 1978).

Boudene et al. (1977) exposed rats to ^{210}Pb-labeled aerosols at a level of 1 µg label/m^3 and 10 µg/m^3, the majority of the particles being 0.1-0.5 µm in size. At 1 hour, 30 percent of the label had left the lung; by 48 hours 90 percent was gone.

Bianco et al. (1974) used ^{212}Pb aerosol (≦0.2 µm) inhaled briefly by dogs and found a clearance half-time from the lung of approximately 14 hours. Greenhalgh et al. (1979) found that direct instillation of ^{203}Pb-labeled lead nitrate solution into the lungs of rats led to an uptake of approximately 42 percent within 30 minutes, compared with an uptake rate of 15 percent within 15 minutes in the rabbit. These instillation data are consistent with the report of Pott and Brockhaus (1971), who noted that intratracheal instillation of lead in solution (as bromide) or suspension (as oxide) serially over 8 days resulted in systemic lead levels in tissues indistinguishable from injected lead. Rendall et al. (1975) found that the movement of lead into blood of baboons inhaling a lead oxide (Pb_3O_4) was more rapid and resulted in higher levels when coarse (1.6 µm mean diameter) rather than fine (0.8 µm mean diameter) particles were used. This suggests that considerable fractions of both size particles were eventually lodged in the gut, where absorption of lead tends to be higher in baboons than in other animal species (Pounds et al., 1978). In addition, the larger particles appear to move more rapidly to the gut.

10.2.2 Gastrointestinal Absorption of Lead

Gastrointestinal absorption of lead mainly involves uptake from food and beverages as well as lead deposited in the upper respiratory tract and eventually swallowed. It also includes ingestion of non-food material, primarily in children via normal mouthing activity and pica. Two issues of concern with lead uptake from the gut are the comparative rates of such absorption in developing vs. adult organisms, including humans, and how the bioavailability of lead affects such uptake.

10.2.2.1 Human Studies. Based on the long-term metabolic studies with adult volunteers, Kehoe (1961a,b,c) estimated that approximately 10 percent of dietary lead is absorbed from the gut of humans. According to Gross (1981), there can be considerable variation of various balance parameters among subjects. These studies did not take into account the contribution of biliary clearance of lead into the gut, which would have affected measurements for both absorption and total excretion. Chamberlain et al. (1978) also determined that the level of endogenous fecal lead is approximately 50 percent of urinary lead values. Chamberlain et al. (1978) have estimated that 15 percent of dietary lead is absorbed, if the amount of endogenous fecal lead is taken into account.

(range 5-17); the mean absorption rate determined from metabolic balance studies was 53 percent. Ziegler et al. (1978) carried out a total of 89 metabolic balance studies with 12 normal infants aged 2 weeks to 2 years. Diets were closely controlled and lead content was measured. Two discrete studies were carried out and in the first, 51 balance studies using 9 children furnished a mean absorption rate of 42.7 percent. In the second study, 6 children were involved in 38 balance studies involving dietary lead intake at 3 levels. For all daily intakes of 5 μg Pb/kg/day or higher, the mean absorption rate was 42 percent. At low levels of lead intake data were variable, with some children apparently in negative balance, probably due to the difficulty in controlling low lead intake.

In contrast to these studies, Barltrop and Strehlow (1978) found that with children hospitalized as orthopedic or "social" admissions, the results were highly variable. A total of 104 balance studies were carried out in 29 children ranging in age from 3 weeks to 14 years. Fifteen of the subjects were in net negative balance, with an average dietary absorption of -40 percent and, when weighted by number of balance studies, -16 percent.

It is difficult to closely compare these data with those of Ziegler et al. (1978). Subjects were inpatients, represented a much greater age range, and were not classified in terms of mineral nutrition or weight change status. As an urban pediatric group, the children in this study may have had higher prior lead exposure so that the "washout" phenomenon (Kehoe, 1961a,b,c; Gross, 1981) may have contributed to the highly variable results. The calculated mean daily lead intake in the Barltrop and Strehlow group (6.5 μg/kg/day) was lower than those for all but one study group described by Ziegler et al. (1978). In the latter study it appears that data for absorption became more variable as the daily lead intake was lowered. Finally, in those children classified as orthopedic admissions, it is not clear that skeletal trauma was without effect on lead equilibrium between bone and other body compartments.

As typified by the results of the NHANES II survey (Mahaffey et al., 1979), children at 2-3 years of age show a small peak in blood lead during childhood. The question arises whether this peak indicates an intrinsic biological factor, such as increased absorption or retention when compared with older children, or whether this age group is exposed to lead in some special way. Several studies are relevant to the question. Zielhuis et al. (1978) reported data for blood lead levels in 48 hospitalized Dutch children ranging in age from 2 months to 6 years. Children up to 3 years old had a mean blood lead level of 11.9 μg/dl vs. a level of 15.5 in children aged 4-6 years. A significant positive relationship between child age and blood lead was calculated ($r = 0.44$, $p < 0.05$). In the Danish survey by Nygaard et al. (1977), a subset of 126 children representing various geographical areas and age groups yielded the following blood lead values by mean age group: children ($N = 8$) with a mean age of 1.8 years had a mean blood lead of 4.3 μg/dl; those with a mean age of 3.7-3.9 had values ranging from 5.6 to 8.3 μg/dl children 4.6-4.8 years of age had a range of 9.2 to 10 μg/dl.

Following the Kehoe studies, a number of reports determined gastrointestinal (GI) absorption using both stable and radioisotopic labeling of dietary lead. Generally, these reports support the observation that in the adult human there is limited absorption of lead when taken with food. Harrison et al. (1969) determined a mean absorption rate of 14 percent for three adult subjects ingesting ^{203}Pb-labeled lead in diet, a figure in accord with the results of Hursh and Suomela (1968). Chamberlain et al. (1978) studied the absorption of ^{203}Pb in two forms (as the chloride and as the sulfide) taken with food. The corresponding absorption rates were 6 percent (sulfide) and 7 percent (chloride), taking into account endogenous fecal excretion. Using adult subjects who ingested the stable isotope ^{204}Pb in their diet, Rabinowitz et al. (1974) reported an average gut absorption of 7.7 percent. In a later study, Rabinowitz et al. (1980) measured an absorption rate of 10.3 percent.

A number of recent studies indicate that lead ingested under fasting conditions is absorbed to a much greater extent than when it is taken with or incorporated into food. For example, Blake (1976) measured a mean absorption rate of 21 percent when 11 adult subjects ingested ^{203}Pb-labeled lead chloride several hours after breakfast. Chamberlain et al. (1978) found that lead uptake in six subjects fed ^{203}Pb as the chloride was 45 percent after a fasting period, compared to 6 percent with food. Heard and Chamberlain (1982) obtained a rate of 63.3 percent using a similar procedure with eight subjects. Rabinowitz et al. (1980) reported an absorption rate of 35 percent in five subjects when ^{204}Pb was ingested after 16 hours of fasting. To the extent that lead in beverages is ingested between meals, these isotope studies support the observations of Barltrop (1975) and Garber and Wei (1974) that beverage lead is absorbed to a greater extent than is lead in food.

The relationship of lead bioavailability in the human gut to the chemical/biochemical form of lead can be determined from available data, although interpretation is complicated by the relatively small amounts given and the presence of various components of food already present in the gut. Harrison et al. (1969) found no difference in lead absorption from the human gut when lead isotope was given either as the chloride or incorporated into alginate. Chamberlain et al. (1978) found that labeled lead as the chloride or sulfide was absorbed to the same extent when given with food, while the sulfide form was absorbed at a rate of 12 percent compared with 45 percent for the chloride when given under fasting conditions. Rabinowitz et al. (1980) obtained similar absorption rates for the chloride, sulfide, or cysteine complex forms when administered with food or under fasting conditions. Heard and Chamberlain (1982) found no difference in absorption rate when isotopic lead (^{203}Pb) was given with unlabeled liver and kidney or when the label was first incorporated into these organs.

Three studies have focused on the question of differences in gastrointestinal absorption rates between adults and children. Alexander et al. (1973) carried out 11 balance studies with 8 children, aged 3 months to 8 years. Intake averaged 10.6 μg Pb/kg body weight/day

10.2.2.2 Animal Studies. Lead absorption via the gut of various adult experimental animal species appears to resemble that for the adult human, on the order of 1-15 percent in most cases. Kostial and Kello (1979), Kostial et al. (1978), and Kostial et al. (1971) reported a value of 1 percent or less in adult rats maintained on commercial rat chow. These studies were carried out using radioisotopic tracers. Similarly, Barltrop and Meek (1975) reported an absorption rate of 4 percent in control diets, while Aungst et al. (1981) found the value to range from 0.9 to 6.9 percent, depending on the level of lead given in the diet. In these rat studies, lead was given with food. Quarterman and Morrison (1978) administered ^{203}Pb label in small amounts of food to adult rats and found an uptake rate of approximately 2 percent at 4 months of age. Pounds et al. (1978) obtained a value of 26.4 percent with four adult Rhesus monkeys given ^{210}Pb by gastric intubation. The higher rate, relative to the rat, may reflect various states of fasting at time of intubation or differences in dietary composition (vide infra), two factors that affect rates of absorption.

As seen above with human subjects, fasting appears to enhance the rate of lead uptake in experimental animals. Garber and Wei (1974) found that fasting markedly enhanced gut uptake of lead in rats. Forbes and Reina (1972) found that lead dosing by gastric intubation of rats yielded an absorption rate of 16 percent, which is higher than other data for the rat. It is likely that intubation was done when there was little food in the gut. The data of Pounds et al. (1978), as described above, may also suggest a problem with giving lead by gastric intubation or with water as opposed to mixing it with food.

The bioavailability of lead in the gastrointestinal tract of experimental animals has been the subject of a number of reports. The designs of these studies differed in accordance with how "bioavailability" is defined by different investigators. In some cases, the dietary matrix was kept constant, or nearly so, while the chemical or physical form of the lead was varied. By contrast, other data described the effect of changes in bioavailability as the basic diet matrix was changed. The latter case is complicated by the simultaneous operation of lead-nutrient interactive relationships, which are described in Section 10.5.2 within this chapter.

Allcroft (1950) observed comparable effects when calves were fed lead in the form of the phosphate, oxide, or basic carbonate ($PbCO_3 \cdot Pb(OH)_2$), or incorporated into wet or dry paint. By contrast, lead sulfide in the form of finely ground galena ore was less toxic. Criteria for relative effect included kidney and blood lead levels and survival rate over time.

In the rat, Barltrop and Meek (1975) carried out a comparative absorption study using lead in the form of the acetate as the reference substance. The carbonate and thallate were absorbed to the greatest extent, while absorption of the sulfide, chromate, napthenate, and octoate was 44-67 percent of the reference agent. Gage and Litchfield (1968, 1969) found that lead napthenate and chromate can undergo considerable absorption from the rat gut when

incorporated into dried paint films, although less than when given with other vehicles. Ku et al. (1978) found that lead in the form of the acetate or as a phospholipid complex was equally absorbed from the GI tract of both adult and young rats at a level of 300 ppm. Uptake was assessed by weight change, tissue levels of lead, and urinary aminolevulinic acid levels.

In a study relevant to the problem of lead bioavailability in soils and dusts, particularly in exposed children, Dacre and Ter Haar (1977) compared the effects of lead as acetate with lead contained in roadside soil and in house paint soil, at a level of approximately 50 ppm, in commercial rat chow. Uptake of lead was indexed by weight change, tissue lead content, and inhibition of ALA-D activity. There was no significant difference in any of these parameters across the three groups, suggesting that neither the geochemical matrix in the soils or the various chemical forms--basic carbonate in paint soil, and the oxide, carbonate, and basic carbonate in roadside soil--affect lead uptake.

These data are consistent with the behavior of lead in dusts upon acid extraction as reported by Day et al. (1979), Harrison (1979), and Duggan and Williams (1977). In the Day et al. study, street dust samples from England and New Zealand were extracted with hydrochloric acid over the pH range of 0-5. At an acidity that may be equalled by gastric secretions, i.e., pH of 1, approximately 90 percent of the dust lead was solubilized. Harrison (1979) noted that at this same acidity, up to 77 percent of Lancaster, England, street dust lead was soluble, while an average 60 percent solubility was seen in London dust samples (Duggan and Williams, 1977). Because gastric solubilization must occur for lead in these media to be absorbed, the above data are useful in determining relative risk.

Kostial and Kello (1979) compared the absorption of ^{203}Pb from the gut of rats maintained on commercial rat chow vs. rats fed such "human" diets as baby foods, porcine liver, bread, and cow's milk. Absorption in the latter cases varied from 3 to 20 percent, compared with <1.0 percent with rat chow. This range of uptake for the non-chow diet compares closely with that reported for human subjects (vide supra). Similarly, Jugo et al. (1975a) observed that rats maintained on fruit diets had an absorption rate of 18-20 percent. It would appear, then, that the generally observed lower absorption of lead in the adult rat vs. the adult human is less reflective of a species difference than of a dietary difference.

Barltrop and Meek (1979) studied the relationship of particle size of lead in two forms--as the metal or as lead octoate or chromate in powdered paint films--to the amount of gut absorption in the rat and found that there was an inverse relationship between uptake and particle size for both forms.

A number of studies have documented that the developing animal absorbs a relatively greater fraction of ingested lead than does the adult, thus supporting those studies that have shown this age dependency in humans. For example, the adult rat absorbs approximately 1 percent lead or less when contained in diet vs. a corresponding value 40-50 times greater in the

rat pup (Kostial et al., 1971, 1978; Forbes and Reina, 1972). In the rat, this difference persists through weaning (Forbes and Reina, 1972), at which point uptake resembles that of adults. Part of this difference can be ascribed to the nature of the diet (mother's milk vs. regular diet), although it should be noted that the extent of absorption enhancement with milk vs. rat chow in the adult rat (Kello and Kostial, 1973) falls short of what is seen in the neonate. An undeveloped, less selective intestinal barrier may also exist in the rat neonate. In non-human primates, Munro et al. (1975) observed that infant monkeys absorbed 65-85 percent via the gut vs. 4 percent in adults. Similarly, Pounds et al. (1978) noted that juvenile Rhesus monkeys absorbed approximately 50 percent more lead than adults.

The question of the relationship of level of lead intake through the GI tract and rate of lead absorption was addressed by Aungst et al. (1981), who exposed adult and suckling rats to doses of lead by intubation over the range 1-100 mg Pb/kg or by variable concentrations in drinking water. With both age groups and both forms of oral exposure, lead absorption as a percentage of dose decreased, suggesting a saturation phenomenon for lead transport across the gut wall.

10.2.3 Percutaneous Absorption of Lead

Absorption of inorganic lead compounds through the skin appears to be considerably less significant than the respiratory and gastrointestinal routes of uptake. This is in contrast to the observations for lead alkyls and other organic derivatives (U.S. Environmental Protection Agency, 1977). Uptake of alkyl lead through the skin is discussed in Section 10.7.

Rastogi and Clausen (1976) found that cutaneous or subcutaneous administration of lead napthenate in rat skin was associated with higher tissue levels and more severe toxic effects than was the case for lead acetate. Laug and Kunze (1948) applied lead as the acetate, ortho-arsenate, oleate, and ethyl lead to rat skin and determined that the greatest levels of kidney lead were associated with the alkyl contact.

Moore et al. (1980) studied the percutaneous absorption of ^{203}Pb-labeled lead acetate in cosmetic preparations using eight adult volunteers. Applied in wet or dry forms, absorption was indexed by blood, urine, and whole body counting. Absorption rates ranged from 0 to 0.3 percent, with the highest values obtained when the application sites were scratched. These researchers estimated that the normal use of such preparations would result in an absorption of approximately 0.06 percent.

10.2.4 Transplacental Transfer of Lead

Lead uptake by the human and animal fetus occurs readily, based on such indices as fetal tissue lead measurements and, in the human, cord blood lead levels. Barltrop (1969) and Horiuchi et al. (1959) demonstrated by fetal tissue analysis that placental transfer in the

human occurs by the 12th week of gestation, with increasing fetal lead uptake throughout development. Highest levels occur in bone, kidney, and liver, followed by blood, brain, and heart. Cord blood contains significant amounts of lead, generally correlating with maternal blood values and being slightly but significantly lower than mothers' in concentration (Scanlon, 1971; Harris and Holley, 1972; Gershanik et al., 1974; Buchet et al., 1978; Alexander and Delves, 1981; Rabinowitz and Needleman, 1982).

A cross-sectional study of maternal blood lead carried out by Alexander and Delves (1981) showed that a significant decrease in maternal blood lead occurs throughout pregnancy, a decrease greater than the dilution efffect of the concurrent increase in plasma volume. Hence, during pregnancy there is either an increasing deposition of lead in placental or fetal tissue or an increased loss of body lead via other routes. Increasing absorption by the fetus during gestation, as demonstrated by Barltrop (1969), suggests that the former explanation is a likely one. Hunter (1978) found that summer-born children showed a trend to higher blood lead than those born in the spring, suggesting increased fetal uptake in the summer due to increases in circulating maternal lead. This observation was confirmed in the report of Rabinowitz and Needleman (1982). Ryu et al. (1978) and Singh et al. (1978) both reported that infants born to women having a history of lead exposure had significantly elevated blood lead values at birth

10.3 DISTRIBUTION OF LEAD IN HUMANS AND ANIMALS

A quantitative understanding of the sequence of changes in levels of lead in various body pools and tissues is essential in interpreting measured levels of lead with respect to past exposure as well as present and future risks of toxicity. This section discusses the distribution kinetics of lead in various portions of the body--blood, soft tissues, calcified tissues, and the "chelatable" or toxicologically active body burden--as a function of such parameters as exposure history and age.

A given quantity of lead taken up from the GI tract or the respiratory tract into the bloodstream is initially distributed according to the rate of delivery by blood to the various organs and systems. Lead is then redistributed to organs and systems in proportion to their respective affinities for the element. With consistent exposure for an extended period, a near steady-state of intercompartmental distribution is achieved.

Fluctuations in the near steady-state will occur whenever short-term lead exposures are superimposed on a long-term uptake pattern. Furthermore, the steady-state description is imperfect because on a very short (hourly) time scale, intake is not constant. Lead intake with meals and changes in ambient air lead--outside to inside and vice versa--will cause quick changes in exposure levels which may be viewed as short-term alterations in the small, labile

lead pool. Metabolic stress could remobilize and redistribute body stores, although documentation of the extent to which this happens is very limited (Chisolm and Harrison, 1956).

10.3.1 Lead in Blood

Viewed from different time scales, lead in whole blood may be seen as residing in several distinct, interconnected pools. More than 99 percent of blood lead is associated with the erythrocytes (DeSilva, 1981; Everson and Patterson, 1980; Manton and Cook, 1979) under typical conditions, but it is the very small fraction of lead transported in plasma and extracellular fluid that provides lead to the various body organs (Baloh, 1974).

Most of the erythrocyte lead is bound within the cell, although toxicity of the element to the erythrocyte (Raghavan et al., 1981) is mainly associated with membrane lead content. Within erythrocytes from non-exposed subjects, lead is primarily bound to hemoglobin, in particular HbA_2, which binds approximately 50 percent of cell lead although it comprises only 1-2 percent of total hemoglobin (Bruenger et al., 1973). A further 5 percent is bound to a 10,000-dalton molecular weight fraction, about 20 percent to a much heavier molecule, and about 25 percent is considered "free" or bound to lower weight molecules (Ong and Lee, 1980a; Raghavan and Gonick, 1977). Raghavan et al. (1980) have observed that, among workers exposed to lead, those who develop signs of toxicity at relatively low blood lead levels seem to have a diminished binding of intracellular lead with the 10,000-dalton fraction, suggesting an impaired biosynthesis of a protective species. According to Ong and Lee (1980b), fetal hemoglobin has a higher affinity for lead than adult hemoglobin. Whole blood lead in daily equilibrium with other compartments was found to have a mean life of 35 days (25-day half-life) and a total content of 1.9 mg, based on studies with a small number of subjects (Rabinowitz et al., 1976). Chamberlain et al. (1978) established a similar half-time for ^{203}Pb in blood when volunteers were given the label by ingestion, inhalation, or injection. The inhaled lead studies in adults, described by Griffin et al. (1975), permit calculation of half-times of 28 and 26 days for inhalation of 10.4 and 3.1 μg Pb/m^3 respectively.

Alterations in blood lead levels in response to abrupt changes in exposure apparently occur over somewhat different periods, depending on whether the direction of change is greater or smaller. With increased lead intake, blood lead achieves a new value in approximately 60 days (Griffin et al., 1975; Tola et al., 1973), while a decrease may involve a longer period of time, depending on the magnitude of the past higher exposure (O'Flaherty et al., 1982; Rabinowitz et al. 1977; Gross, 1981). With age, there appears to be a modest increase in blood lead, Awad et al. (1981) reporting an increase of 1 μg for each 14 years of age. In the latter case, particularly with occupational exposure, it appears that the time for re-establishing near steady-state is more dependent upon the extent of lead resorption from bone and the total quantity deposited, extending the "washout" interval.

Lead levels in newborn children are similar to but somewhat lower than those of their mothers: 8.3 vs. 10.4 µg/dl (Buchet et al., 1978) and 11.0 vs. 12.4 µg/dl (Alexander and Delves, 1981). Alexander and Delves (1981) also reported that maternal blood lead levels decrease throughout pregnancy, such decreases being greater than the expected dilution via the concurrent increase in plasma volume. These data are consistent with increasing fetal uptake during gestation (Barltrop, 1969). Increased tissue retention may also be a factor.

Levels of lead in blood are sex-related, adult women invariably showing lower levels than adult males (e.g., Mahaffey et al., 1979). Of interest in this regard is the study of Stuik (1974) showing lower blood lead response in women than in men for an equivalent level of lead intake.

The small but biologically significant lead pool in blood plasma has proven technically difficult to measure reliable values have become available only recently, and (see Chapter 9). Chamberlain et al. (1978) found that injected ^{203}Pb was removed from plasma (and, by inference, extracellular fluid) with a half-life of less than 1 hour. These data support the observation of DeSilva (1981) that lead is rapidly cleared from plasma. Ong and Lee (1980a), in their in vitro studies, found that ^{203}PB is virtually all bound to albumin and that only trace amounts are bound to high weight globulins. It is not possible to state which binding form constitutes an "active" fraction for movement to tissues.

Although Rosen et al. (1974) reported that plasma lead was invariant across a range of whole blood levels, the findings of Everson and Patterson (1980), DeSilva (1981), and Cavalleri et al. (1978) indicate that there is an equilibrium between red cell and plasma, such that levels in plasma rise with levels in whole blood. This is consistent with the data of Clarkson and Kench (1958) who found that lead in the red cell is relatively labile to exchange and a logical prerequisite for a dose-effect relationship in various organs. Ong and Lee (1980c), furthermore, found that plasma calcium is capable of displacing RBC membrane lead, suggesting that plasma calcium is a factor in the cell-plasma lead equilibrium.

10.3.2 Lead Levels in Tissues

Of necessity, various relationships of tissue lead to exposure and toxicity in humans generally must be obtained from autopsy samples, although in some studies biopsy data have been described. There is, then, the inherent question of how such samples adequately represent lead behavior in the living population, particularly in cases where death was preceded by prolonged illness or disease states. Also, victims of fatal accidents are not well characterized as to exposure status, and are usually described as having no "known" lead exposures. Finally, these studies are necessarily cross-sectional in design, and in the case of body accumulation of lead it is assumed that different age groups have been similarly exposed. Some important aspects of the available data include the distribution of lead between soft and

calcifying tissue, the effect of age and development on lead content of soft and mineral tissue, and the relationship between total and "active" lead burdens in the body.

10.3.2.1 Soft Tissues. In humans after age 20 most soft tissues do not show age-related changes in lead levels, in contrast to the case with bone (Barry and Mossman, 1970; Barry, 1975, 1981; Schroeder and Tipton, 1968; Butt et al., 1964). Kidney cortex also shows increases in lead with age that may be associated with formation of lead nuclear inclusion bodies (Indraprasit et al., 1974). Based on these rates of accumulation, the total body burden may be divided into pools that behave differently: the largest and kinetically slowest pool is the skeleton, which accumulates lead with age; and the much more labile lead pool is in soft tissue.

Soft tissue levels generally stabilize in early adult life and show a turnover rate similar to blood, sufficient to prevent accumulation except in the renal cortex, which may be reflecting formation of lead-containing nuclear inclusion bodies (Cramer et al., 1974; Indraprasit et al., 1974). The data of Gross et al. (1975) and Barry (1975) indicate that aortic levels appear to rise with age, although this may reflect entrapment of lead in atherosclerotic deposits. Biliary and pancreatic secretions, while presumably reflecting some of the organ levels, have tracer lead concentrations distinct from either blood or bone pools (Rabinowitz et al., 1973).

For levels of lead in soft tissue, the reports of Barry (1975, 1981), Gross et al. (1975) and Horiuchi et al. (1959) indicate that soft tissue lead content generally is below 0.5 μg/g wet weight, with higher values for aorta and kidney cortex. The higher values in aorta may or may not reflect lead in plaque deposits, while higher kidney levels may be associated with the presence of lead-accumulating tubular cell nuclear inclusions. The relatively constant lead concentration in lung tissue across age groups suggests no accumulation of respired lead and is consistent with data for deposition and absorption (see Section 10.2.2). Brain tissue was generally under 0.2 ppm wet weight and appeared to show no change with increasing age. Since these data were collected by cross-sectional study, age-related changes in the low levels of lead in brain would have been difficult to discern. Barry (1975) found that tissues in a small group of samples from subjects with known or suspected occupational exposure showed higher lead levels in aorta, liver, brain, skin, pancreas, and prostate.

Levels of lead in whole brain are less illuminating to the issue of sensitivity of certain regions within the organ to toxic effects of lead than is regional analysis. The distribution of lead across brain regions has been reported from various laboratories and the relevant data for humans and animals are set forth in Table 10-2. The data of Grandjean (1978) and Niklowitz and Mandybur (1975) for human adults, and those of Okazaki et al. (1963) for autopsy samples from young children who died of lead poisoning, are consistent in showing that lead is selectively accumulated in the hippocampus. The correlation of lead level with

TABLE 10-2. REGIONAL DISTRIBUTION OF LEAD IN HUMANS AND ANIMALS

Species	Exposure status	Relative distribution	Reference
Humans			
Adult Males	Unexposed	Hippocampus ≅ amygdala > medulla oblongata > half brain > optic tract ≅ corpus callosum. Pb correlated with K.	Grandjean, 1978
Children	Fatal lead poisoning	Hippocampus > frontal cortex >> occipital white matter, pons	Okazaki et al., 1963
Child, 2 yrs. old	Fatal lead poisoning	Cortical gray matter > basal gangli > cortical white matter	Klein et al., 1970
Adults	3 subjects unexposed; 1 subject with lead poisoning as child	Hippocampus > cerebellum ≅ temporal lobes > frontal cortex in 3 unexposed subjects; temporal lobes > frontal cortex > hippocampus > cerebellum > in case with prior exposure	Niklowitz and Mandybur, 1975
Animals			
Adult rats	Unexposed	Hippocampus > amygdala >> whole brain	Danscher et al., 1975
Adult rats	Unexposed	Hippocampus had 50 percent of brain lead with a 4:1 ratio of hippocampus:whole brain	Fjerdingstad et al., 1974

TABLE 10-2 (continued)

Species	Exposure status	Relative distribution	Reference
Neonatal rats	Controls and daily i.p. injection, 5.0 or 7.5 mg/kg	In both treated and control animals: cerebellum > cerebral cortex > brainstem + hippocampus	Klein and Koch, 1981
Young dogs	Controls and dietary exposure, 100 ppm; 12 weeks of exposure	Controls: cerebellum ≅ medulla > caudate > occipital gray > frontal gray Exposed: occipital gray > frontal gray ≅ caudate > occipital white ≅ thalamus > medulla > cerebellum	Stowe et al., 1973

potassium level suggests that uptake of lead is greater in cellulated areas. The involvement of the cerebellum in lead encephalopathy in children (see Section 12.4) and in adult intoxication from occupational exposure indicates that the sensitivity of various brain regions to lead as well as their relative uptake characteristics are factors in lead neuropathology.

In adult rats, selective uptake of lead is shown by the hippocampus (Fjerdingstad et al., 1974; Danscher et al., 1975) and the amygdala (Danscher et al., 1975). By contrast, lead-exposed neonate rats show greatest uptake of lead into cerebellum, followed by cerebral cortex, then brainstem plus hippocampus. Hence, there is a developmental difference in lead distribution in the rat with or without increased lead exposure (Klein and Koch, 1981).

In studies of young dogs, unexposed animals showed highest levels in the cerebellum, while lead exposure was associated with selective uptake into gray matter; cerebellar levels were relatively low. Unlike the young rat, then, the distribution of lead in brain regions of dogs appears to be dose-dependent (Stowe et al., 1973).

Barry (1975, 1981) compared lead levels in soft tissues of children vs. adults. Tissue lead of infants under 1 year old was generally lower than in older children, while children aged 1-16 years had values that were comparable to adult women. In the Barry (1981) study, the absolute concentration of lead in brain cortex or the ratios of brain cortex to blood lead levels did not appear to be different in infants or older children compared to adults. Such direct comparisons do not account for relative tissue mass changes with age, but this factor is comparatively less with soft tissue than with the skeletal system (see Section 10.4).

Subcellular distribution of lead in soft tissue is not uniform, with high amounts of lead being sequestered in the mitochondria and nucleus. Cramer et al. (1974) studied renal biopsy tissue in lead workers having exposures of variable duration and observed lead-binding nuclear inclusion bodies in renal proximal tubules of subjects having short exposure, with all showing mitochondrial changes. A considerable body of animal data (see Section 10.3.5) documents the selective uptake of lead into these organelles. Pounds and Wright (1982) describe these organellar pools in kinetic terms as having half-lives of comparatively short duration in cultured rat hepatocytes, while McLachlin et al. (1980) found that rat kidney epithelial cells form lead-sequestering nuclear inclusions within 24 hours.

10.3.2.2 Mineralizing Tissue. Biopsy and autopsy data have shown that lead becomes localized and accumulates in human calcified tissues, i.e., bones and teeth. The accumulation begins with fetal development (Barltrop, 1969; Horiuchi et al., 1959).

Total lead content in bone may exceed 200 mg in men aged 60 to 70 years, but in women the accumulation is somewhat lower. Various investigators (Barry, 1975; Horiguchi and Utsonomiya, 1973; Schroeder and Tipton, 1968; Horiuchi et al., 1959) have documented that approximately 95 percent of total body lead is lodged in bone. These reports not only establish the affinity of bone for lead, but also provide evidence that lead increases in bone until 50-60 years, the

later fall-off reflecting some combination of diet and mineral metabolism changes. Tracer data show accumulation in both trabecular and compact bone (Rabinowitz et al., 1976).

In adults, bone lead is the most inert pool as well as the largest, and accumulation can serve to maintain elevated blood lead levels years after past, particularly occupational, exposure has ended. This accounts for the observation that duration of exposure correlates with the rate of reduction of blood lead after termination of exposure (O'Flaherty et al., 1982). The proportion of body lead lodged in bone is reported to be lower in children than in adults, although concentrations of lead in bone increase more rapidly than in soft tissue during childhood (Barry, 1975, 1981). In 23 children, bone lead was 9 mg, or 73 percent of total body burden vs. 94 percent in adults. Expression of lead in bone in terms of concentration across age groups, however, does not accommodate the "dilution" factor, which is quite large for the skeletal system in children (see Section 10.4).

The isotope kinetic data of Rabinowitz et al. (1976) and Holtzman (1978) indicate biological half-times of lead in bone on the order of several decades, although it appears that there are two bone compartments, one of which is a repository for relatively labile lead (Rabinowitz et al., 1977).

Tooth lead levels also increase with age at a rate proportional to exposure (Steenhout and Pourtois, 1981), and are also roughly proportional to blood lead levels in man (Winneke et al., 1981) and experimental animals (Kaplan et al., 1980). Dentine lead is perhaps the most responsive component of teeth to lead exposure since it is laid down from the time of eruption until the tooth is shed. Needleman and Shapiro (1974) have documented the utility of dentine lead as an indicator of the degree of subject exposure. Fremlin and Edmonds (1980), using alpha particle excitation and micro-autoradiography, have shown dentine zones of lead enrichment related to abrupt changes in exposure. The rate of lead deposition in teeth appears to vary with the type of tooth, being highest in the central incisors and lowest in the molars, a difference that must be taken into account when using tooth lead data for exposure assessment, particularly for low levels of lead exposure (Mackie et al., 1977; Delves et al., 1982).

10.3.3 Chelatable Lead

Mobile lead in organs and systems is potentially more "active" toxicologically in terms of being available to sites of action. Hence, the presence of diffusible, mobilizable, or exchangeable lead may be a more significant predictor of imminent toxicity or recent exposure than total body or whole blood burdens. In reality, however, these would be quite difficult assays.

In this regard, "chelatable" urinary lead has been shown to provide an index of this mobile portion of total body burden. Chelation challenge is now viewed as the most useful probe of undue body burden in children and adults (U.S. Centers for Disease Control, 1978;

World Health Organization, 1977; Chisolm and Barltrop, 1979; Chisolm et al., 1976; Saenger et al., 1982; Hansen et al., 1981), based mainly on the relationship of chelatable lead to indices of heme biosynthesis impairment. In general, the amount of plumburesis associated with chelant challenge is related to the dose and the schedule of administration.

A quantitative description of inputs to the fraction of body lead that is chelatable from various body compartments is difficult to fully define, but it very likely includes a sizable, fairly mobile compartment within bone as well as soft tissues this assertion is based on: 1) the fact that the amount of lead mobilized by chelation is age dependent in non-exposed adults (Araki, 1973; Araki and Ushio, 1982) while blood and soft tissue lead levels are not (Barry, 1975), indicating a lead pool labile to chelation but kinetically distinct from soft tissue; 2) the studies of chelatable lead in animals (Hammond, 1971, 1973) suggesting removal of some bone lead fraction and the response of explanted fetal rat bone lead to chelants (Rosen and Markowitz, 1980); 3) the tracer modeling estimates of Rabinowitz et al. (1977) which suggest a mobile bone compartment; and 4) the complex, non-linear relationship of lead intake by air, food, and water (see Chapter 11) to blood lead, as well as the exponential relationship of chelatable lead to blood lead (Chisolm et al., 1976).

The logarithmic relationship of chelatable lead to blood lead in children (Chisolm et al., 1976) is consistent with the studies of Saenger et al. (1982), who reported that levels of mobilizable lead in "asymptomatic" children with moderate elevations in blood lead were quite similar in many cases to those values obtained in children with signs of overt toxicity. Hansen et al. (1981) reported that lead workers challenged with $CaNa_2EDTA$ showed 24-hour urine lead levels that in many cases exceeded the accepted limit levels even though blood lead was only moderately elevated in many of those workers. The action level corresponded, on the regression curve, to a blood value of 35 µg/dl.

Several reports provide insight into the behavior of labile lead pools in children treated with chelating agents over varying periods of time. Treatment regimens using $CaNa_2EDTA$ or $CaNa_2EDTA$ + BAL for up to 5 days have been invariably associated with "rebound" in blood lead, ascribed to a redistribution of lead among mobile lead compartments (Chisolm and Barltrop, 1979). Marcus (1982) reported that 41 children given oral D-penicillamine for 3 months showed a significant drop in blood lead by 2 weeks (mean initial value of 53.2 µg/dl) then a slight rise that was within measurement error with a peak at 4 weeks, and a fall at 6 weeks, followed by no further change at a blood lead of 36 µg/dl. Hence, there was a near steady-state at an elevated level for 10 of the 12 weeks with continued treatment. This observation may indicate that re-exposure was occurring, with oral penicillamine and ingested lead leading to increased lead uptake, as seen by Jugo et al. (1975a). However, Marcus states that an effort was made to limit further lead intake as much as possible. From these reports, it appears that a re-equilibration does occur, varying in characteristics with type

and duration of chelation. The rebound seen in short-term treatment with $CaNa_2EDTA$ or $CaNa_2EDTA$ + BAL, although attributed to soft tissue, could well include a shift of lead from a larger mobile bone compartment to soft tissues and blood. The apparent steady state between the blood lead pool and other compartments that is achieved in the face of plumburesis, induced by D-penicillamine (Marcus, 1982), suggests a rather sizable labile body pool which, in quantitative terms, would appear to exceed that of soft tissue alone.

10.3.4 Mathematical Descriptions of Physiological Lead Kinetics

In order to account for observed kinetic data and make predictive statements, a variety of mathematical models have been suggested, including those describing "steady state" conditions. Tracer experiments have suggested compartmental models of lead turnover based on a central blood pool (Holtzman, 1978; Rabinowitz et al., 1976; Batschelet et al., 1979). These experiments have hypothesized well-mixed, interconnected pools and have utilized coupled differential equations with linear exponential solutions to predict blood and tissue lead exchange rates. Were lead to be retained in these pools in accordance with a power-law distribution of residence times, rather than being uniform, a semi-Markov model would be more appropriate (Marcus, 1979).

Lead pools with more rapid turnover than whole blood (on the order of minutes) have been detected within isolated cells (Pounds and Wright, 1982). Evidence of an extracellular lead pool in humans exists in observations of lead plasma (DeSilva, 1981) and urine (Rabinowitz et al., 1974) after oral lead exposure, as well as from ^{203}Pb studies using injection, ingestion, and inhalation exposure routes (Chamberlain and Heard, 1981). No single model has been developed to utilize what has been learned about lead behavior in these highly labile pools existing around and within permanent and concentrated sites.

Extant steady-state models are also deficient, not only because they are based on small numbers of subjects but also because there may be a dose dependency for some of the interpool transfer coefficients. In this case, a non-linear dose-indicator response model would be more appropriate when considering changes in blood lead levels. For example, the relationship between blood lead and air lead (Hammond et al., 1981) as well as that for diet (United Kingdom Central Directorate on Environmental Pollution, 1982) and tap drinking water (Sherlock et al., 1982) are all non-linear in mathematical form. In addition, alterations in nutritional status or the onset of metabolic stresses can complicate steady-state relationships.

The above discussions of both the non-linear relationship of intake to the blood lead pool and the non-linear relationship of chelatable, or toxicologically active, lead to blood levels logically indicate that intake at elevated levels can add substantially to this chelatable pool and be substantially unrecognized in blood lead measurements.

10.3.5 Animal Studies

The relevant questions to be asked of animal data are those that cannot be readily or fully satisfied in human subjects: (1) What is the effect of exposure level on distribution within the body at specific time points? (2) What is the relationship of age or developmental stage on the distribution of lead in organs and systems, particularly the nervous system? (3) What are the relationships of physiological stress and nutritional status to the redistribution kinetics? (4) Can the relationship of chelatable lead to such indicator lead pools as blood be defined better?

Administration of a single dose of lead to rats produces high initial lead concentrations in soft tissues, which then fall rapidly as the result of excretion and transfer to bone (Hammond, 1971), while the distribution of lead appears to be independent of the dose. Castellino and Aloj (1964) reported that single dose exposure of rats to lead was associated with a fairly constant ratio of red cell to plasma, a rapid distribution to tissues and relatively higher uptake in liver, kidney, and particularly bone. Lead loss from organs and tissues follow first-order kinetics except for bone. The data of Morgan et al. (1977), Castellino and Aloj (1964), and Keller and Doherty (1980a) document that the skeletal system in rats and mice is the kinetically rate-limiting step in whole-body lead clearance.

Subcellular distribution studies involving either tissue fractionation after in vivo lead exposure or in vitro data document that lead is preferentially sequestered in the nucleus (Castellino and Aloj, 1964; Goyer et al., 1970) and mitochondrial fractions (Castellino and Aloj, 1964; Barltrop et al., 1974) of cells from lead-exposed animals. Lead enrichment in the mitochondrion is consistent with the high sensitivity of this organelle to the toxic effects of lead.

The neonatal animal seems to retain proportionately higher levels of tissue lead compared with the adult (Goldstein et al., 1974; Momcilović and Kostial, 1974; Mykkänen et al., 1979; Klein and Koch, 1981) and shows slow decay of brain lead levels while other tissue levels significantly decrease over time. This appears to be the result of enhanced entry by lead due to a poorly developed brain barrier system in the developing animals, as well as enhanced body retention in the young animals. The effects of such changes as metabolic stress and nutritional status have been noted in the literature. Keller and Doherty (1980b) have documented that tissue redistribution of lead, specifically bone lead mobilization, occurs in lactating female mice, both lead and calcium transfer occurring from mother to pups. Changes in lead movement from body compartments, particularly bone, with changes in nutrition are described in Section 10.5.

In studies with rats that are relevant both to the issue of chelatable lead vs. lead indicators in humans and to the relative lability of lead in the young vs. the adult, Jugo et al. (1975b) and Jugo (1980) studied the chelatability of lead in neonate vs. adult rats and

its lability in the erythrocyte. Challenging young rats with metal chelants yielded proportionately lower levels of urinary lead than in the adult, a finding that has been ascribed to tighter binding of lead in the young animal (Jugo et al., 1975b). In a related observation, the chelatable fraction of lead bound to erythrocytes of young animals given ^{203}Pb was approximately 3-fold greater than in the adult rat (Jugo, 1980), although the fraction of dose in the cells was higher in the suckling rat. The difference in the suckling rat erythrocyte regarding the binding of lead and relative content compared with the adult may be compared with the Ong and Lee's (1980b) observation that human fetal hemoglobin binds lead more avidly than does mature hemoglobin.

10.4 LEAD EXCRETION AND RETENTION IN HUMANS AND ANIMALS

Dietary lead in humans and animals that is not absorbed passes through the gastrointestinal tract and is eliminated with feces, as is that deposited fraction of air lead that is swallowed and not absorbed. Lead absorbed into the blood stream and not retained is excreted through the renal and gastrointestinal tracts, the latter by biliary clearance. The amounts appearing in urine and feces appear to be a function of such factors as species, age, and differences in dosing.

10.4.1 Human Studies

Booker et al. (1969) found that ^{212}Pb injected into two adult volunteers led to initial appearance of the label first in urine (4.4 percent of dose in 24 hours), then in both urine and feces in approximately equal amounts. By use of the stable isotope ^{204}Pb, Rabinowitz et al. (1973) reported that urinary and fecal excretion of the label amounted to 38 and 8 µg/day in adult subjects, accounting for 76 and 16 percent, respectively, of the measured recovery. Fecal excretion was thus approximately twice that of all the remaining modes of excretion: hair, sweat, and nails (8 percent).

Perhaps the most detailed study of lead excretion in adult humans was done by Chamberlain et al. (1978), who used ^{203}Pb administered by injection, inhalation and ingestion. Following injection or oral intake, the amounts in urine (Pb-U) and feces (Pb-Fe, endogenous fecal lead) were compared for the two administration routes. Endogenous fecal lead was 50 percent of that in urine, or a 2:1 ratio of urinary/fecal lead, after allowing for increased transit time of fecal lead through the GI tract.

Based on the metabolic balance and isotope excretion data of Kehoe (1961a,b,c), Rabinowitz et al. (1976), and Chamberlain et al. (1978), as well as some recalculations of the Kehoe and Rabinowitz data by Chamberlain et al. (1978), it appears that short-term lead excretion amounts to 50-60 percent of the absorbed fraction, the balance moving primarily to bone

TABLE 10-3. COMPARATIVE EXCRETION AND RETENTION RATES[a] IN ADULTS AND INFANTS

	Children[b]	Adult group A[c]	Adult group B[d]
Dietary intake (μg/kg)	10.76	3.63	3.86
Fraction absorbed[e]	0.46 (0.55)[f]	0.15[g]	0.15[g]
Diet lead absorbed (μg/kg)	4.95 (5.92)	0.54	0.58
Air lead absorbed (μg/kg)	0.20	0.21	0.11
Total absorbed lead (μg/kg	5.15 (6.12)	0.75	0.68
Daily urinary Pb (μg/kg)	1.00	0.47	0.34
Ratio: urinary/absorbed Pb	0.19 (0.16)	0.62	0.50
Endogenous fecal Pb	0.5 (1.56)[h]	0.24[i]	0.17[i]
Total excreted Pb	1.50 (2.56)	0.71	0.51
Ratio: total excreted/ absorbed Pb	0.29 (0.42)	0.92	0.75
Fraction of intake retained	0.34 (0.33)	0.01	0.04

[a] μg/kg-day.
[b] Ziegler et al., 1978.
[c] Rabinowitz et al., 1977.
[d] Thompson, 1971, and estimates of Chamberlain et al., 1978.
[e] Corrected for endogenous fecal Pb; Pb-Fe = 0.5 x Pb-U.
[f] Corrected for endogenous fecal Pb at extrapolated value from Ziegler et al., 1978.
[g] Corrected for Pb-Fe.
[h] Extrapolated value for endogenous fecal Pb of 1.56.
[i] For a ratio of 0.5, Pb-Fe/Pb-U.

with some subsequent fraction, (approximately half) of this stored amount eventually being excreted. The rapidly excreted fraction was determined by Chamberlain et al. (1978) to have an excretion half-time of about 19 days. This is consistent with the estimates of Rabinowitz et al. (1976), who expressed clearance in terms of mean-times. Mean-times are multiplied by ln 2 (0.693) to arrive at half-times. The similarity of blood ^{203}Pb half-times with that of body excretion noted by Chamberlain et al. (1978) indicates a steady rate of clearance from the body.

The age dependency of lead excretion rates in humans has not been well studied, for all of the above lead excretion data involved only adults. Table 10-3 combines available data from adults and infants for purposes of comparison. Intake, urine, fecal, and endogenous fecal lead data from two studies involving adults and one report with infants are used. For consistency in the adult data, 70 kg is used as an average adult weight, and a Pb-Fe/Pb-U value of 0.5 used. Lead intake, absorption, and excretion are expressed as μg Pb/kg/day. For the Ziegler et al. (1978) data with infants, endogenous fecal lead excretion is calculated using the adult ratio as well as the extrapolated value of 1.5 μg Pb/kg/day. The respiratory intake value for the infants is an upper value (0.2 μg Pb/m^3), since Ziegler et al. found air lead to be <0.2 μg/m^3. In comparison with the two representative adult groups, infants appear to have a lower total excretion rate, although the excretion of endogenous fecal lead may be higher than for adults.

Lead is accumulated in the human body with age, mainly in bone, up to approximately 60 years of age, when a decrease occurs with changes in intake as well as in bone mineral metabolism. Total accumulation by 60 years of age ranges up to approximately 200 mg (see review by Barry, 1978), although occupational exposure can raise this figure several-fold (Barry, 1975). Holtzman (1978) has reviewed the available literature on studies of lead retention in bone. In normally exposed humans a biological half-time of approximately 17 years has been calculated, while data for uranium miners yield a range of 1320-7000 days (4-19 years). Chamberlain et al. (1978) have estimated life-time averaged daily retention at 9.5 μg using data of Barry (1975). Within shorter time frames, however, retention can vary considerably due to such factors as disruption of the individual's equilibrium with lead intake at a given level of exposure, the differences between children and adults, and, in elderly subjects, the presence of osteoporosis (Gross and Pfitzer, 1974).

Lead labeling experiments, such as those of Chamberlain et al. (1978), indicate a short-term or initial retention of approximately 40-50 percent of the fraction absorbed, much of which is by bone. It is difficult to determine how much lead resorption from bone will eventually occur using labeled lead, given the extremely small fraction of labeled to unlabeled lead (i.e., label dilution) that would exist. Based on the estimates of Kehoe (1961a,b,c), the Gross (1981) evaluation of the Kehoe studies, the Rabinowitz et al. (1976) study, the

Chamberlain et al. (1978) assessments of the aforementioned reports, and the data of Thompson (1971), approximately 25 percent of the lead absorbed daily undergoes long-term bone storage.

The above estimates relate either to adults or to long-term retention over most of an individual's lifetime. Studies with children and developing animals (see Section 10.4.2) indicate lead retention in childhood can be higher than in adults. By means of metabolic balance studies, Ziegler et al. (1978) obtained a retention figure (as percentage of total intake) of 31.5 percent for infants, while of Alexander et al. (1973) provided an estimate of 18 percent. Corrected retention data for both total and absorbed intake for the pediatric subjects of Ziegler et al. (1978) are shown in Table 10.3, using the two values for endogenous fecal excretion as noted. Barltrop and Strehlow (1978) calculated a net negative lead retention in their subjects, but problems in comparing this report with the others were noted above. Given the increased retention of lead in children relative to adults, as well as the greater rate of lead intake on a body weight basis, increased uptake in soft tissues and/or bone is indicated.

Barry (1975, 1981) measured the lead content of soft and mineral tissue in a small group of autopsy samples from children 16 years of age and under, and noted that average soft tissue values were comparable to those in female adults, while mean bone lead values were lower than in adults. This suggests that bone in children has less retention capacity for lead than adults. It should be noted, however, that "dilution" of bone lead will occur because of the significant growth rate of the skeletal system through childhood. Trotter and Hixon (1974) studied changes in skeletal mass, density, and mineral content as a function of age, and noted that skeletal mass increases exponentially in children until the early teens, increases less up to the early 20s, levels off in adulthood, and then slowly decreases. From infancy to the late teens, bone mass increases up to 40-fold. Barry (1975) noted an approximate doubling in bone lead concentration over this interval, indicating that total skeletal lead had actually increased 80-fold, and obtained a mean total bone lead content up to 16 years of approximately 8 mg, compared with a value of approximately 18 mg estimated from both the bone concentrations in his study at different ages and the bone growth data of Trotter and Hixon (1974). In a later study (Barry, 1981), autopsy samples from infants and children between 1 and 9 years old showed an approximate 3.5-fold increase in mean bone concentrations across the three bone types studied, compared with a skeletal mass increase from 0-6 mos. to 3-13 years old of greater than 10-fold, for an estimated increase in total lead of approximately 35-fold. Five reports (see Barry, 1981) noted age vs. tissue lead relationships indicating that overall bone lead levels in infants and children were less than in adults, whereas while 4 reports observed comparable levels in children and adults.

If one estimates total daily retention of lead in the infants studied by Ziegler et al. (1978), using a mean body weight of approximately 10 kg and the corrected retention rate in Table 10.3, one obtains a total daily retention of approximately 40 μg Pb. By contrast, the

total reported or estimated skeletal lead accumulated between 2 and 14 years is 8-18 mg (vide supra), which averages out to a daily long-term retention of 2.0-4.5 μg/day or 6-13 percent of total retention. It may be the case that lead retention is highest in infants up to about 2 years of age (the subjects of the Ziegler et al. study), then decreases in older children. The mean retention in the Alexander et al. (1973) study was 18 percent, about half that seen by Ziegler et al. (1978). This difference is possibly due to the greater age range in the former study.

"Normal" blood lead levels in children either parallel adult males or are approximately 30 percent greater than adult females (Chamberlain et al., 1978), indicating (1) that the soft tissue lead pool in very young children is not greatly elevated and thus, (2) that there is a huge labile lead pool in bone which is still kinetically quite distinct from soft tissue lead or (3) that in young children, blood lead is a much less reliable indicator of greatly elevated soft tissue or labile bone lead than is the case with adults. Barry (1981) found that soft tissue lead levels were comparable in infants ≤1 year old and children 1-5 and 6-9 years old.

Given the implications of the above discussion, that retention of lead in the young child is higher than in adults and possibly older children, while at the same time their skeletal system is less effective for long-term lead sequestration, the very young child is at greatly elevated risk to a toxicologically "active" lead burden. For a more detailed discussion, see Chapter 13.

10.4.2 Animal Studies

In rats and other experimental animals, both urinary and fecal excretion appear to be important routes of lead removal from the organism; the relative partitioning between the two modes is species and dose dependent. Morgan et al. (1977), injected ^{203}Pb into adult rats and noted that lead initially appeared in urine, followed by equivalent elimination by both routes; by 5 days, lead was proportionately higher in feces. Castellino and Aloj (1964), using ^{210}Pb, observed that fecal excretion was approximately twice that of urine (35.7 vs. 15.9 percent) by 14 days. In the report of Klaassen and Shoeman (1974), relative excretion by the two routes was seen to be dose-dependent up to 1.0 mg/kg, being much higher by biliary clearance into the gut. At 3.0 mg/kg, approximately 90 percent of the excreted amount was detected in feces. The relatively higher proportion appearing in feces in the studies of Castellino and Aloj (1964) and Klaassen and Shoeman (1974), compared with the results of Morgan et al. (1977), is possibly due to the use of carrier dosing, since Morgan et al. (1977) used carrier-free injections. Hence, it appears that increasing dose does favor biliary excretion, as noted by Klaassen and Shoeman (1974).

With regard to species differences, Klaassen and Shoeman (1974) found that the amount of biliary clearance in dogs was about 2 percent of that in rats, while rabbits showed 50 percent of the rate of the rat at equivalent dosing. These data for the dog are in contrast to the results of Lloyd et al. (1975), who observed 75 percent of the excreted lead eliminated through biliary clearance. It should be noted that the latter researchers used carrier-free label while the other investigators used injections with carrier at 3.0 mg Pb/kg levels. In mice, Keller and Doherty (1980a) observed that the cumulative excretion rate of ^{210}Pb in urine was 25-50 percent of that in feces. In nonhuman primates, Cohen (1970) observed that baboons excreted lead at the rate of 40 percent in feces and 60 percent in urine. Pounds et al. (1978) noted that the Rhesus monkey lost 30 percent of lead by renal excretion and 70 percent in feces. This may also be reflecting a carrier dosing difference.

The extent of total lead excretion in experimental animals given labeled lead orally or parenterally varies, in part due to the time frames for post-exposure observation. In the adult rat, Morgan et al. (1977) found that 62 percent of injected ^{203}Pb was excreted by 6 days. By 8 days, 66 percent of injected ^{203}Pb was eliminated in the adult rats studied by Momcilović and Kostial (1974), while the ^{210}Pb excretion data of Castellino and Aloj (1964) for the adult rat showed 52 percent excreted by 14 days. Similar data were obtained by Klaassen and Shoeman (1974). Lloyd et al. (1975) found that dogs excreted 52 percent of injected lead label by 21 days, 83 percent by 1 year, and 87 percent by 2 years. In adult mice (Keller and Doherty, 1980a), 62 percent of injected lead label was eliminated by 50 days. In the nonhuman primate, Pounds et al. (1978) measured approximately 18 percent excretion in adult Rhesus monkeys by 4 days.

Kinetic studies of lead elimination in experimental animals indicate that excretion is described by two or more components. From the elimination data of Momcilović and Kostial (1974), Morgan et al. (1977) estimated that in the rat the excretion curve obeys a two-component exponential expression with half-times of 21 and 280 hours. In dogs, Lloyd et al. (1975) found that excretion could be described by three components, i.e., a sum of exponentials with half-times of 12 days, 184 days, and 4951 days. Keller and Doherty (1980a) reported that the half-time of whole-body clearance of injected ^{203}Pb consisted of an initial rapid and a much slower terminal component, the latter having a half-time of 110 days in the adult mouse.

The excretion rate dependency on dose level has been investigated in several studies. Although Castellino and Aloj (1964) saw no difference in total excretion rate when label was injected with 7 or 100 µg of carrier, Klaassen and Shoeman (1974) did observe that the excretion rate by biliary tract was dose dependent at 0.1, 1.0, and 3.0 mg Pb/kg (urine values were not provided for obtaining estimates of total excretion). Momcilović and Kostial (1974) saw increased rate of excretion into urine over the added carrier range of 0.1 to 2.0 µg Pb with no change in fecal excretion. In the report of Aungst et al. (1981) there was no change in

excretion rate in the rat over the injected lead dosing range of 1.0 to 15.0 mg/kg. It thus appears that rat urinary excretion rates are dose-dependent over a narrow range less than <7 μg, while elimination of lead through biliary clearance is dose-dependent up to an exposure level of 3 mg Pb/kg.

Lead movement from lactating animals to their offspring via milk constitutes both a route of excretion for the mother and a route of exposure to lead for the young. Investigations directed at this phenomenon have examined both prior-plus-ongoing maternal lead exposure during lactation and the effects of immediate prior treatment. Keller and Doherty (1980b) exposed two groups of female rats to ^{210}Pb-labeled lead: one group for 105 days before mating; the second before and during gestation and nursing. During lactation, there was an overall loss of lead from the bodies of the lactating females compared with controls while the femur ash weights were inversely related to level of lead excretion, indicating that such enhancement is related to bone mineral metabolism. Lead transfer via milk was approximately 3 percent of maternal body burden, increasing with continued lead exposure during lactation. Lorenzo et al. (1977) found that blood lead in nursing rabbits given injected lead peaks rather rapidly (within 1 hour), while milk lead shows a continuous increase for about 8 days, at which point its concentration of lead is 8-fold higher than blood. This indicates that lead transfer to milk can occur against a concentration gradient in blood. Momcilović (1978) and Kostial and Momcilović (1974) observed that transfer of ^{203}Pb in the late stage of lactation occurs readily in the rat, with higher overall excretion of lead in nursing vs. control females. Furthermore, it appeared that the rate of lead movement to milk was dose-dependent over the added lead carrier range of 0.2-2.0 μg Pb.

The comparative retention of lead in developing vs. adult animals has been investigated in several studies using rats, mice, and nonhuman primates. Momcilović and Kostial (1974) compared the kinetics of lead distribution in suckling vs. adult rats after injection of ^{203}Pb. Over an 8-day interval, 85 percent of the label was retained in the suckling rat, compared with 34 percent in the adult. Keller and Doherty (1980a) compared the levels of ^{210}Pb in 10-day-old mice and adults, noting from the clearance half-times (vide supra) that lead retention was greater in the suckling animals than in the adults. In both adult and young mice, the rate of long-term retention was governed by the rate of release of lead from bone, indicating that in the mouse, skeletal lead retention in the young is greater than in the adult. With infant and adult monkeys orally exposed to ^{210}Pb, Pounds et al. (1978) observed that at 23 days the corresponding amounts of initial dose retained were 92.7 and 81.7 percent, respectively.

The studies of Rader et al. (1981; 1982) are of particular interest as they not only demonstrate that young experimental animals continue to show greater retention of lead in tissue when exposure occurs after weaning, but also that such retention occurs in terms of

either uniform exposure (Rader et al., 1981) or uniform dosing (Rader et al., 1982) when compared with adult animals. With uniform exposure, 30-day-old rats given lead in drinking water showed significantly higher lead levels in blood and higher percentages of dose retained in brain, femur, and kidney, as well as higher indices (ALA-U, EP) of hematopoietic impairment when compared with adult animals. As a percentage of dose retained, tissues in the young animals were approximately 2-3-fold higher. In part, the difference is due to a higher ingestion rate of lead. However, in the uniform dosing study where this was not the case, an increased retention of lead still prevailed, the amount of lead in brain being approximately 50 percent higher in young vs. adult animals. Comparison of values in terms of percent retained is more meaningful for such assessments, because the factor of changes in organ mass (see above) is taken into account. Delayed excretion in the young animal may reflect an immature excretory system or a tighter binding of lead in various body compartments.

10.5 INTERACTIONS OF LEAD WITH ESSENTIAL METALS AND OTHER FACTORS

Deleterious agents, particularly toxic metals such as lead, do not express their toxicokinetic or toxicological behavior in a physiological vacuum, but rather are affected by interactions of the agent with a variety of biochemical factors such as nutrients. Growing recognition of this phenomenon and its implications for lead toxicity in humans have prompted a number of studies, many of them recent, that address both the scope and mechanistic nature of such interactive behavior.

10.5.1 Human Studies

In humans, the interactive behavior of lead and various nutritional factors is appropriately viewed as being particularly significant for children, since this age group is not only particularly sensitive to lead's effects, but also represents the time of greatest flux in relative nutrient status. Such interactions occur against a backdrop of rather widespread deficiencies in a number of nutritional components in children. While such deficiencies are more pronounced in lower income groups, they exist in all socioeconomic strata. Mahaffey and Michaelson (1980) have summarized the three nutritional status surveys carried out in the United States for infants and young children: the Preschool Nutrition Survey, the Ten State Nutrition Survey, and the National Health Assessment and Nutritional Evaluation Survey (NHANES I). The most recent body of data of this type is the NHANES II study (Mahaffey et al., 1979), although the dietary information from it has yet is to be reported. In the older surveys, iron deficiency was the most common nutritional deficit in children under 2 years of age, particularly children from low-income groups. Reduced vitamin C intake was noted in about one-third of the children, while sizable numbers of them had significantly reduced intakes of

calcium. Owen and Lippmann (1977) reviewed the regional surveys of low-income groups within Hispanic, white, and black populations. In these groups, iron deficiency was a common finding, while low intakes of calcium and vitamins A and C were observed regularly. Hambidge (1977) concluded that zinc intake in low-income groups is generally inadequate, relative to recommended daily allowances.

Available data from a number of reports document the association of lead absorption with suboptimal nutritional status. Mahaffey et al. (1976) summarized their studies showing that children with blood lead greater than 40 μg/dl had significantly ($p < 0.01$) lower intake of phosphorus and calcium compared with a control group, while iron intake in the two groups was comparable. This study involved children 1-4 years old from an inner-city, low-income population, with close matching for all parameters except the blood lead level. Sorrell et al. (1977), in their nutritional assessment of 1- to 4-year-old children with a range of blood lead levels, observed that blood lead content was inversely correlated with calcium intake, while children with blood lead levels >60 μg/dl had significantly ($p < 0.001$) lower intakes of calcium and vitamin D.

Rosen et al. (1981) found that children with elevated blood lead (33-120 μg/dl) had significantly lower serum concentrations of the vitamin D metabolite 1,25-$(OH)_2$D ($p < 0.001$) compared with age-matched controls, and showed a negative correlation of serum 1,25-$(OH)_2$D with lead over the range of blood leads measured. These observations and animal data (Barton et al., 1978a, see Section 10.5.2) may suggest an increasingly adverse interactive cycle of 1,25-$(OH)_2$D, lead, and calcium in which lead reduces biosynthesis of the vitamin D metabolite. This then leads to reduced induction of calcium binding protein (CaBP), less absorption of calcium from the gut, and greater uptake of lead, thus increasing uptake of lead and further reducing metabolite levels. Barton et al. (1978a) isolated two mucosal proteins in rat intestine, one of which bound mainly lead and was not vitamin D-stimulated; the second bound mainly calcium and was under vitamin control. The authors suggested direct site binding competition between lead and calcium in these proteins. Hunter (1978) investigated the possible interactive role of seasonal vitamin D biosynthesis in adults and children; it is a common observation that lead poisoning occurs more often in summer than in other seasons (see Hunter, 1977, for review). In children, seasonality accounts for 16 percent of explained variance of blood lead in black children, 12 percent in Hispanics, and 4 percent in whites. More recently, it has been documented that there is no seasonal variation in circulating levels of 1,25-$(OH)_2$D the metabolite that affects the rate of lead absorption from the GI tract (Chesney et al., 1981). These results suggest that seasonality is related to changes in exposure.

Johnson and Tenuta (1979) determined that calcium intake was negatively correlated ($r = -0.327$, $p < 0.05$) with blood lead in 43 children aged 1-6 years. The high lead group also consumed less zinc than children with lower blood levels. Yip et al. (1981) found that 43

children with elevated blood lead (>30 µg/dl) and EP (>35 µg/dl) had an increased prevalence of iron deficiency as these two parameters increased. Children classed as CDC Ib and II had a 79 percent deficiency rate, while those in Class III were all iron-deficient. Chisolm (1981) demonstrated an inverse relationship between "chelatable" iron and chelatable body lead levels as indexed by urinary ALA levels in 66 children with elevated blood lead. Watson et al. (1980) reported that adult subjects who were iron-deficient (determined from serum ferritin measurement) showed a lead absorption rate 2-3 times greater than subjects who were iron replete. In a group of 13 children, Markowitz and Rosen (1981) reported that the mean serum zinc levels in children with plumbism were significantly below the values seen in normal children. Chelation therapy reduced the mean level even further. Chisolm (1981) reported that there was an inverse relationship between ALA-U and the amount of "chelatable" or systemically active zinc in 66 children challenged with EDTA and having blood lead levels ranging from 45 to 60 µg Pb/dl. These two studies suggest that zinc status is probably as important an interactive modifier of lead toxicity as is either calcium or iron.

The role of nutrients in lead absorption has been reported in several metabolic balance studies for both adults and children. Ziegler et al. (1978), in their investigations of lead absorption and retention in infants, observed that lead retention was inversely correlated with calcium intake, expressed either as intake percentage ($r = -0.284$, $p < 0.01$) or on a weight basis ($r = -0.279$, $p < 0.01$). Of interest is the fact that the range of calcium intake measured was within the range considered adequate for infants and toddlers by the National Research Council (National Academy of Sciences, National Research Council, 1974). These data also support the premise that severe deficiency need not be present for an interactive relationship to occur. Using adults, Heard and Chamberlain (1982) monitored the uptake of ^{203}Pb from the gut in eight subjects as a function of the amounts of dietary calcium and phosphorus. Without supplementation with either of these minerals in fasting subjects, the label absorption rate was approximately 60 percent, compared with 10 percent with 200 mg calcium plus 140 mg phosphorus, the amounts present in an average meal. Calcium alone reduced uptake by a factor of 1.3 and phosphorus alone by 1.2; both together yielded a reduction factor of 6. This work suggests that insoluble calcium phosphate is formed and co-precipitates any lead present. This interpretation is supported by animal data (see Section 10.5.2).

10.5.2 Animal Studies

Reports of lead-nutrient interactions in experimental animals have generally described such relationships in terms of a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the recent data are concerned with the impact of dietary levels of calcium, iron, phosphorus, and vitamin D. Furthermore, some investigators have attempted to elucidate the site(s) of interaction as well as the mechanism(s)

governing the interactions. Lead's interactions involve the effect of the nutrient on lead uptake, as well as lead's effect on nutrients; the focus of this discussion is on the former. These interaction studies are tabulated in Table 10-4.

10.5.2.1 Interactions of Lead with Calcium. The early report of Sobel et al. (1940) noted that variation of dietary calcium and other nutrients affected the uptake of lead by bone and blood in animals. Subsequent studies by Mahaffey-Six and Goyer (1970) in the rat demonstrated that a considerable reduction in dietary calcium was necessary from (0.7 percent to 0.1 percent), at which level blood lead was increased 4-fold, kidney lead content was elevated 23-fold, and relative toxicity (Mahaffey et al., 1973) was increased. The changes in calcium necessary to alter lead's effects in the rat appear to be greater than those seen by Ziegler et al. (1978) in young children, indicating species differences in terms of sensitivity to basic dietary differences, as well as to levels of all interactive nutrients. These observations in the rat have been confirmed by Kostial et al. (1971), Quarterman and Morrison (1975), Barltrop and Khoo (1975), and Barton et al. (1978a). The inverse relationship between dietary calcium and lead uptake has also been noted in the pig (Hsu et al., 1975), horse (Willoughby et al., 1972), lamb (Morrison et al., 1977), and domestic fowl (Berg et al., 1980).

The mechanism(s) governing lead's interaction with calcium operate at both the gut wall and within body compartments. Barton et al. (1978a), using everted duodenal sac preparations in the rat, reported that: (1) interactions at the gut wall require the presence of intubated calcium to affect lead label absorption - (pre-existing calcium deficiency in the animal and no added calcium have no effect on lead transport); (2) animals having calcium deficiency show increased retention of lead rather than absorption (confirmed by Quarterman et al., 1973); and (3) lead transport may be mediated by two mucosal proteins, one of which has high molecular weight, a high proportion of bound lead, and is affected in extent of lead binding with changes in lead uptake. The second protein binds mainly calcium and is vitamin D-dependent.

Smith et al. (1978) found that lead is taken up at a different site in the duodenum of rats than is calcium but absorption does occur at the site of phosphate uptake, suggesting a complex interaction of phosphorus, calcium, and lead. This is consistent with the data of Barltrop and Khoo (1975) for rats and the data of Heard and Chamberlain (1982) for humans, thus showing that the combined action of the two mineral nutrients is greater than the sum of either's effects.

Mykkänen and Wassermann (1981) observed that lead uptake in the intestine of the chick occurs in 2 phases: a rapid uptake (within 5 minutes) followed by a rate-limiting slow transfer of lead into blood. Conrad and Barton (1978) have observed a similar process in the rat.

TABLE 10-4. EFFECT OF NUTRITIONAL FACTORS ON LEAD UPTAKE IN ANIMALS

Factor	Species	Index of effect	Interactive effect	Reference
Calcium	Rat	Lead in tissues and effect severity at low levels of dietary calcium	Low dietary calcium (0.1%) increases lead absorption and severity of effects	Mahaffey-Six and Goyer, 1970; Mahaffey et al., 1973
Calcium	Pig	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Hsu et al., 1975
Calcium	Horse	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Willoughby et al., 1972
Calcium	Lamb	Lead in tissue at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Morrison et al., 1977
Calcium	Rat	Lead retention	Retention increased in calcium deficiency	Barton et al., 1978a
Iron	Rat	Tissue levels and relative toxicity of lead	Iron deficiency increases lead absorption and toxicity	Mahaffey-Six and Goyer, 1972
Iron	Rat	Lead absorption in everted duodenal sac preparation	Reduction in intubated iron increases lead absorption; increased levels decrease lead uptake	Barton et al., 1978b
Iron	Mouse	Lead retention	Iron deficiency has no effect on lead retention	Hamilton, 1978

TABLE 10-4. (continued)

Factor	Species	Index of effect	Interactive effect	Reference
Iron	Rat	In utero or milk transfer of lead in pregnant or lactating rats	Iron deficiency increases both in utero and milk transfer of lead to sucklings	Cerklewski, 1980
Phosphorus	Rat	Lead uptake in tissues	Reduced P increased ^{203}Pb uptake 2.7-fold	Barltrop and Khoo, 1975
Phosphorus	Rat	Lead retention	Low dietary P enhances lead retention; no effect on lead resorption in bone	Quarterman and Morrison, 1975
Phosphorus	Rat	Lead retention	Low dietary P enhances both lead retention and deposition in bone	Barton and Conrad, 1981
Vitamin D	Rat	Lead absorption using everted sac techniques	Increasing vitamin D increases intubated lead abosrption	Smith et al., 1978
Vitamin D	Rat	Lead absorption using everted sac techniques	Both low and excess levels of vitamin D increase lead uptake by affecting motility	Barton et al., 1980
Lipid	Rat	Lead absorption	Increases in lipid (corn oil) content up to 40 percent enhances lead absorption	Barltrop and Khoo, 1975
Protein	Rat	Lead uptake by tissues	Both low and high protein in diet increase lead absorption	Barltrop and Khoo, 1975

TABLE 10-4. (continued)

Factor	Species	Index of effect	Interactive effect	Reference
Protein	Rat	Body lead retention	Low dietary protein either reduces or does not affect retention in various tissues	Quarterman et al., 1978b
Protein	Rat	Tissue levels of lead	Casein in diet increases lead uptake compared to soybean meal	Anders et al., 1982
Milk components	Rat	Lead absorption	Lactose-hydrolyzed milk does not increase lead absorption, but ordinary milk does	Bell and Spickett, 1981
Milk components	Rat	Lead absorption	Lactose in diet enhances lead absorption compared to glucose	Bushnell and DeLuca, 1981
Zinc/Copper	Rat	Lead absorption	Low zinc in diets increases lead absorption	Cerklewski and Forbes, 1976; El-Gazzar et al., 1978
Zinc/Copper	Rat	Lead transer *in utero* and in milk during lactation	Low-zinc diet of mother increases lead transfer *in utero* and in maternal milk	Cerklewski, 1979
Zinc/Copper	Rat	Lead absorption	Low copper in diet increases lead absorption	Klauder et al., 1973; Klauder and Petering, 1975

Hence, there is either a saturation process occurring, i.e., carrier-mediated transport, or simply lead precipitation in the lumen. In the former case, calcium interacts to saturate the carrier proteins as isolated by Barton et al. (1978a) or may precipitate lead in the lumen by initial formation of calcium phosphate.

Quarterman et al. (1978a) observed that calcium supplementation of the diet above normal also resulted in increased body retention of lead in the rat. Because both deficiency (Barton et al., 1978a) and excess in calcium intake enhance retention, two sites of influence on retention are suggested. Goyer (1978) has suggested that body retention of lead in calcium deficiency, i.e., reduced excretion rate, may be due to renal impairment, while Quarterman et al. (1978a) suggest that excess calcium suppresses calcium resorption from bone, hence also reducing lead release.

10.5.2.2 Interactions of Lead with Iron. Mahaffey-Six and Goyer (1972) reported that iron-deficient rats had increased tissue levels of lead and manifested greater toxicity compared with control animals. This uptake change was seen with but minor alterations in hematocrit, indicating a primary change in lead absorption over the time of the study. Barton et al. (1978b) found that dietary restriction of iron, using ^{210}Pb and everted sac preparations in the rat, led to enhanced absorption of iron; iron loading suppressed the extent of lead uptake, using normal intake levels of iron. This suggests receptor binding competition at a common site, consistent with the isolation by these workers of two iron-binding mucosa fractions. While iron level of diet affects lead absorption, the effect of changes in lead content in the gut on iron absorption is not clear. Barton et al. (1978b) and Dobbins et al. (1978) observed no effect of lead in the gut on iron absorption in the rat, while Flanagan et al. (1979) reported that lead reduced iron absorption in mice.

In the mouse, Hamilton (1978) found that body retention of ^{203}Pb was unaffected by iron deficiency, using intraperitoneal administration of the label, while gastric intubation did lead to increased retention. Animals with adequate iron showed no changes in lead retention at intubation levels of 0.01 to 10 nM. Cerklewski (1980) observed that lead transfer both in utero and in milk to nursing rats was enhanced when dams were maintained from gestation through lactation on low iron diets compared with controls.

10.5.2.3 Lead Interactions with Phosphate. The early studies of Shelling (1932), Grant et al. (1938), and Sobel et al. (1940) documented that dietary phosphate influenced the extent of lead toxicity and tissue retention of lead in animals, with low levels enhancing those parameters while excess intake retarded the effects. More recently, Barltrop and Khoo (1975) reported that reduced phosphate increased the uptake of ^{203}Pb approximately 2.7-fold compared with controls. Quarterman and Morrison (1975) found that low dietary phosphate enhanced lead retention in rats but had no effect on skeletal lead mobilization nor was injected lead label affected by such restriction. In a related study, Quarterman et al. (1978a) found that

doubling of the nutrient over normal levels resulted in lowering of lead absorption by approximately half. Barton and Conrad (1981) found that reduced dietary phosphorus increased the retention of labeled lead and deposition in bone, in contrast to the results of Quarterman and Morrison (1975). Increasing the intraluminal level of phosphorus reduced lead absorption, possibly by increasing intraluminal precipitation of lead as the mixed lead/calcium phosphate. Smith et al. (1978) reported that lead uptake occurs at the same site as phosphate, suggesting that lead absorption may be more related to phosphate than calcium transport.

10.5.2.4 Interactions of Lead with Vitamin D. Several studies had earlier indicated that a positive relationship might exist between dietary vitamin D and lead uptake, resulting in either greater manifestations of lead toxicity or a greater extent of lead uptake (Sobel et al., 1938, 1940). Using the everted sac technique and testing with ^{210}Pb, Smith et al. (1978) observed that increasing levels of intubated vitamin D in the rat resulted in increased absorption of the label, with uptake occurring at the distal end of the rat duodenum, the site of phosphorus uptake and greatest stimulation by the vitamin. Barton et al. (1980) used ^{210}Pb to monitor lead absorption in the rat under conditions of normal, deficient, and excess amounts of dietary vitamin D. Lead absorption is increased with either low or excess vitamin D. This apparently occurs because of increased retention time of fecal mass containing the lead due to alteration of intestinal motility rather than because of direct enhancement of mucosal uptake rate. Hart and Smith (1981) reported that vitamin D repletion of diet enhanced lead absorption (^{210}Pb) in the rat, while also enhancing femur and kidney lead uptake when the label was given by injection.

10.5.2.5 Interactions of Lead with Lipids. Barltrop and Khoo (1975) observed that varying the lipid (corn oil) content of rat diet from 5 up to 40 percent resulted in an increase of lead in blood 13.6-fold higher compared with the normal level. Concomitant increases were observed in lead levels in kidney, femur, and carcass. Reduction of dietary lipid below the 5 percent control figure was without effect on lead absorption rate. As an extension of this earlier work, Barltrop (1982) has noted that the chemical composition of the lipid is a significant factor in affecting lead absorption. Study of triglycerides of saturated and unsaturated fatty acids showed that polyunsaturated, trilinolein increased lead absorption by 80 percent in rats, when given as 5 or 10 percent loadings in diet, compared with monounsaturated triolein or any of the saturates in the series tricaproin to tristearin.

10.5.2.6 Lead Interaction with Protein. Quarterman et al. (1978b) have drawn attention to one of the inherent difficulties of measuring lead-protein interactions, i.e., the effect of protein on both growth and the toxicokinetic parameters of lead. Der et al. (1974) found that reduction of dietary protein, from 20 to 4 percent, led to increased uptake of lead in rat tissues, but the approximately 6-fold reduction in body weight over the interval of the study makes it difficult to draw any firm conclusions. Barltrop and Khoo (1975) found that lead

(^{203}Pb) uptake by rat tissue could be enhanced with either suboptimal or excess levels of protein in diet. Quarterman et al. (1978b) reported that retention of labeled lead in rats maintained on a synthetic diet containing approximately 7 percent protein was either unaffected or reduced compared with controls, depending on tissues taken for study.

It appears that not only levels of protein but also the type of protein affects tissue levels of lead. Anders et al. (1982) found that rats maintained on either of two synthetic diets varying only as to having casein or soybean meal as the protein source showed significantly higher lead levels in the casein group.

10.5.2.7 Interactions of Lead with Milk Components. For many years, milk was recommended prophylactically for lead poisoning among lead workers (Stephens and Waldron, 1975). More recent data, however, suggest that milk may actually enhance lead uptake. Kello and Kostial (1973) found that rats maintained on milk diets absorbed a greater amount of ^{203}Pb than those having access to commercial rat chow. This was ascribed to relatively lower levels of certain nutrients in milk compared with the rat chow. These observations were confirmed by Bell and Spickett (1981), who also observed that lactose-hydrolyzed milk was less effective than the ordinary form in promoting lead absorption, suggesting that lactose may be the enhancing principle. Bushnell and DeLuca (1981) demonstrated that lactose significantly increased lead (^{210}Pb) absorption and tissue retention by weanling rats by comparing diets identical in all respects except for carbohydrate source. These results provide one rationale for why nursing mammals tend to absorb greater quantities of lead than adults; lactose is the major carbohydrate source in suckling rats and is known to enhance the uptake of many essential metals.

10.5.2.8 Lead Interactions with Zinc and Copper. The studies of Cerklewski and Forbes (1976) and El-Gazzar et al. (1978) documented that zinc-deficient diets promote lead absorption in the rat, while repletion with zinc reduces lead uptake. The interaction continues within the body, particularly with respect to ALA-D activity (see Chapter 11). In a study of zinc-lead interactions in female rats during gestation and lactation, Cerklewski (1979) observed that zinc-deficient diets resulted in more transfer of lead through milk to the pups as well as reduced litter body weights.

Klauder et al. (1973) reported that low dietary copper enhanced lead absorption in rats fed a high lead diet (5000 ppm). These observations were confirmed by Klauder and Petering (1975) at a level of 500 ppm lead in diet. These researchers subsequently observed that reduced copper enhanced the hematological effects of lead (Klauder and Petering, 1977), and that both copper and iron deficiencies must be corrected to restore hemoglobin levels to normal.

10.6 INTERRELATIONSHIPS OF LEAD EXPOSURE, EXPOSURE INDICATORS, AND TISSUE LEAD BURDENS

Information presented so far in this chapter sets forth the quantitative and qualitative aspects of lead toxicokinetics, including the compartmental modeling of lead distribution in vivo, and leads up to the critical issue of the various interrelationships of lead toxicokinetics to lead exposure, toxicant levels in indicators of such exposure, and exposure-target tissue burdens of lead.

Chapter 11 (Sections 11.4, 11.5, 11.6) discusses the various experimental and epidemiological studies relating the relative impact of various routes of lead exposure on blood lead levels in human subjects, including the description of mathematical models for such relationships. In these sections, the basic question is: what is the mathematical relationship of lead in air, food, water, etc. to lead in blood? This question is descriptive and does not address the biological basis of the observed relationships. Nor does it consider the implications for adverse health risk in the sequence of exposure leading from external lead to lead in some physiological indicator to lead in target tissues.

For purposes of discussion, this section separately considers 1) the temporal characteristics of physiological indicators of lead exposure, 2) the biological aspects of the relationship of external exposure to internal indicators of exposure, and 3) internal indicator-tissue lead relationships, including both steady-state lead exposure and abrupt changes in lead exposure. The relationship of internal indicators of body lead, such as blood lead, to biological indicators such as EP or urinary ALA is discussed in Chapter 13, since any comparative assessment of the latter should follow the chapter on biological effects, Chapter 12.

10.6.1 Temporal Characteristics of Internal Indicators of Lead Exposure

The biological half-time for blood lead or the non-retained fraction of body lead is relatively short (see Sections 10.3 and 10.4); thus, a given blood or urine lead value reflects rather recent exposure. In cases where lead exposure can be reliably assumed to have occurred at a given level, a blood lead value is more useful than in cases where some intermittent, high level of exposure may have occurred. The former most often occurs with occupational exposure, while the latter is of particular relevance to young children.

Accessible mineralizing tissue, such as shed teeth, extend the time frame for assessing lead exposure from weeks or several months to years (Section 10.3), since teeth accumulate lead up to the time of shedding or extraction. Levels of lead in teeth increase with age in proportion to exposure (Steenhout and Pourtois, 1981). Furthermore, tooth levels are proportional to blood lead levels in humans (Shapiro et al., 1978) and animals (Kaplan et al., 1980). The technique of Fremlin and Edmonds (1980), employing micro-autoradiography of irradiated teeth, permits the identification of dentine zones high in lead content, thus allowing the disclosure of past periods of abrupt increases in lead intake.

While levels of lead in shed teeth are more valuable than blood lead in assessing exposure at more remote time points, such information is retrospective in nature and would not be of use in monitoring current exposure. In this case, serial blood lead measurements must be employed. With the development of methodology for in situ measurement of tooth lead in children (described in Chapter 9), serial in situ tooth analysis in tandem with serial blood lead determining would provide comparative data for determination of both time-concordant blood/tooth relationships as well as which measure is the better indicator of ongoing exposure. Given the limitations of an indicator such as blood lead in reflecting lead uptake in target organs, as discussed below, it may well be the case that the rate of accumulation of lead in teeth, measured in situ, is a better index of ongoing tissue lead uptake than is blood lead. This aspect merits further study, especially as Shapiro et al. (1978) were able to demonstrate the feasibility of using in situ tooth lead analysis in a large group of children screened for lead exposure.

10.6.2 Biological Aspects of External Exposure-Internal Indicator Relationships

Information provided in Chapter 11 as well as the critique of Hammond et al. (1981) indicate that the relationship of levels of lead in air, food, and water to lead in blood is curvilinear, with the result that as "baseline" blood lead rises, i.e., as one moves up the curve, the relative change in the dependent variable, blood lead, per unit change of lead in some intake medium (such as air) becomes smaller. Conversely, as one proceeds down the curve with reduction in "baseline" lead, the corresponding change in blood lead becomes larger. One assumption in this "single medium" approach is that the baseline is not integrally related to the level of lead in the particular medium being studied. This assumption is not necessarily appropriate in the case of air vs. food lead, nor, in the case of young children, air lead vs. total oral intake of the element.

Hammond et al. (1981) have noted that the shape of the blood lead curves seen in human subjects is similar to that discernible in certain experimental animal studies with dogs, rats, and rabbits (Azar et al., 1973; Prpić-Majić et al., 1973). Also, Kimmel et al. (1980) exposed adult female rats to lead at four levels in drinking water for 6-7 weeks and reported values of blood lead that showed curvilinear relationship to the dose levels. Over the dosing range of 5 to 250 ppm in water, the blood lead range was 8.5 to 31 µg/dl. In a related study (Grant et al., 1980) rats were exposed to lead in utero, through weaning, and up to 9 months of age at the dosing range used in the Kimmel et al. study the weanlings, 0.5 to 250 ppm in the dams' drinking water until weaning of pups; then the same levels in the weanlings' drinking water) showed a blood lead range of 5 to 67 µg/dl. It may be assumed in all of the above studies that lead in the various dosing groups was near or at equilibrium within the various body compartments.

The biological basis of the curvilinear relationship of blood lead to lead intake does not appear to be due to reduced absorption or enhanced excretion of the element with changes in exposure level. In other words, a decrease in the ratio of blood lead to medium lead as blood lead increases cannot be taken to indicate reduced uptake rate of lead into target tissues. In the study of Prpić-Majić et al. (1973), dosing was by injection so that the GI absorption rate of lead was not a factor. Azar et al. (1973) reported values for urinary lead across the dosing groups that indicated the excretion rate for the 10, 50, 100, and 500 ppm dietary lead groups was fairly constant. As suggested by Hammond et al. (1981), the shape of the blood lead curves in the context of external exposure is probably related to the tissue distribution of lead. Other supporting evidence is the relationship of blood lead to chelatable lead and that of tissue burden to dosing level as discussed below.

10.6.3 Internal Indicator-Tissue Lead Relationships

In living human subjects it is not possible to directly determine tissue burdens of lead (or relate these levels to adverse effects associated with target tissue) as a function of lead intake. Instead, measurement of lead in an accessible indicator such as blood, along with determination of some biological indicator of impairment, e.g., ALA-U or EP, is used.

Evidence continues to accumulate in both the clinical and experimental animal literature that the use of blood lead as an indicator has limitations in reflecting both the amounts of lead in target tissues and the temporal changes in tissue lead with changes in exposure. Perhaps the best example of the problem is the relationship of blood lead to chelatable lead (see Section 10.3.3). Presently, measurement of the plumburesis associated with challenge by a single dose of a chelating agent such as $CaNa_2EDTA$ is considered the best measure of the mobile, potentially toxic, fraction of body lead in children and adults (Chisolm et al., 1976; U.S. Centers for Disease Control, 1978; Chisolm and Barltrop, 1979; Hansen et al., 1981).

Chisolm et al. (1976) have documented that the relationship of blood lead to chelatable lead is curvilinear, such that a given incremental increase in blood lead is associated with an increasingly larger increment of mobilizable lead. The problems associated with this curvilinear relationship in exposure assessment are typified by the recent reports of Saenger et al. (1982) concerning children and Hansen et al. (1981) concerning on adult lead workers. In the former study, it was noted that significant percentages of children having mild to moderate lead exposure, as discernible by blood lead and EP measurements, were found to have urinary outputs of lead upon challenge with $CaNa_2EDTA$ qualifing them for chelation therapy under CDC guidelines. In adult workers, Hansen et al. (1981) observed that a sizable fraction of subjects with only modest elevations in blood lead excreted lead upon $CaNa_2EDTA$ challenge significantly exceeding the upper end of normal. This occurred at blood lead levels of 35 µg/dl and above.

The biological basis for the non-linearity of the relationship between blood lead and chelatable lead, appears in a major part, to be the existence of a sizeble pool of lead in bone that is labile to chelation. Evidence pointing to this was summarized in Section 10.3.3. The question of how long any lead in this compartment of bone remains labile to chelation has been addressed by several investigators in studies of both children and adults. The question is relevant to the issue of the utility of EDTA challenge in assessing evidence for past lead exposure.

Chisolm et al. (1976) found that a group of adolescent subjects (N = 55; 12-22 yrs old), who had a clinical history of lead poisoning as young children and whose mean blood lead was 22.1 µg/dl at the time of study, yielded chelatable lead values that placed them on the same regression curve as a second group of young children with current elevations of blood lead. The results with the adolescent subjects did not provide evidence that they might have had a past history of lead poisoning. According to the authors, this suggests that chelatable lead at the time of excessive exposure was not retained in a pool that remained labile to chelation years later, but underwent subsequent excretion or transfer to the inert compartment of bone. One problem with drawing conclusions from this study is that all of the adolescents apparently had one or more courses of chelation therapy and were removed to housing where re-exposure would be minimal as part of their clinical management after lead poisoning was diagnosed. One must assume that chelation therapy removed a significant portion of the mobile lead burden and placement in lead-free housing reduced the extent of any further exposure. The obvious question is how would this group of adolescents compare with subjects who had excessive chronic lead exposure as young children but who did not require or receive chelation therapy?

Former lead workers challenged with $CaNa_2EDTA$ show chelatable lead values that are significantly above normal years after workplace exposure ceases (e.g., Alessio et al., 1976; Prêrovskà and Teisinger, 1970). In the case of former lead workers, blood lead also remains elevated, suggesting that the mobile lead pool in bone remains in equilibrium with blood.

The closer correspondence of chelatable lead with actual tissue lead burdens, compared to blood lead, is also reflected in a better correlation of this parameter with such biological indicators of impairment as EP. Saenger et al. (1982), in the study noted above, found that the only significant correlation with erythrocyte protoporphyrin was obtained with the µM Pb/mM EDTA ratio. Similarly, Alessio et al. (1976) found that EP in former lead workers was more significantly correlated with chelatable lead than with blood lead.

Consideration of both the intake vs. blood lead and the blood lead vs. chelatable lead curves leads to the prediction that the level of lead exposure per se is more closely related to tissue lead burden than is blood lead; this appears to be the case in experimental animals. Azar et al. (1973) and Grant et al. (1980) reported that levels of lead in brain, kidney, and femur followed more of a direct proportionality with the level of dosing than with blood lead.

Finally, there is the question of how adequately an internal indicator such as blood lead reflects changes in tissue burden when exposure changes abruptly. In the study of Björklund et al. (1981), lead levels in both blood and brain were monitored over a 6-week period in rats exposed to lead through their drinking water. Blood lead rose rapidly by day 1, during which time brain lead content was only slightly elevated. After day 1, the rate of increase in blood lead began to taper off while brain lead began to rise in a near-linear fashion up to the end of the experiment. From day 7 to 21, blood lead increased from approximately 45 to 55 μg/dl, while brain lead increased approximately 2-fold.

Abrupt reduction in exposure similarly appears to be associated with a more rapid response in blood than in soft tissues, particularly brain. Goldstein and Diamond (1974) reported that termination of intravenous administration of lead to 30-day-old rats resulted in a 7-fold drop of lead in blood by day 7. At the same time, there was no significant decrease in brain lead. A similar difference in brain vs. blood response was reported by Momcliović and Kostial (1974).

In all of the above studies, it may be seen that blood lead was of limited value in reflecting changes in the brain, which is, for children, the significant target organ for lead exposure. With abrupt increases in exposure level, the problem concerns a much more rapid approach to steady-state in blood than in brain. Conversely, the biological half-time for lead clearance from blood in the young rats of both the Goldstein and Diamond (1974) and Momcilović and Kostial (1974) studies was much less than it appeared to be for lead movement from brain.

Despite the limitations in indexing tissue burden and exposure changes, blood lead remains the one measure that can reliably demonstrate the relationship of various effects.

10.7 METABOLISM OF LEAD ALKYLS

The lower alkyl lead compounds used as gasoline additives, tetraethyl lead (TEL) and tetramethyl lead (TML), are much more toxic, i.e., neurotoxic, on an equivalent dose basis than inorganic lead. These agents are emitted in auto exhaust and their rate of environmental degradation depends on such factors as sunlight, temperature, and ozone levels. There is also some concern that organolead compounds may result from biomethylation in the environment (see Chapter 6). Finally, there appears to be a problem with the practice among children of sniffing leaded gasoline. The available information dealing with metabolism of lead alkyls is derived mainly from experimental animal studies, workers exposed to the agents and cases of lead alkyl poisoning.

10.7.1 Absorption of Lead Alkyls in Humans and Animals

The respiratory intake and absorption of TEL and TML in the vapor state was investigated by Heard et al. (1979), who used human volunteers inhaling ^{203}Pb-labeled TEL and TML. Initial lung deposition rates were 37 and 51 percent for TEL and TML, respectively. Of these amounts, 40 percent of TEL was lost by exhalation within 48 hours, while the corresponding figure for TML was 20 percent. The remaining fraction was absorbed. The effect of gasoline vapor on these parameters was not investigated. In this study Mortensen (1942) reported that adult rats inhaling TEL labeled with ^{203}Pb (0.07-7.00 mg TEL/1) absorbed 16-23 percent of the fraction reaching the alveoli. Gasoline vapor had no effect on the absorption rates.

Respiratory absorption of organolead bound to particulate matter has not been specifically studied as such. According to Harrison and Laxen (1978), TEL or TML does not adher to particulate matter to any significant extent, but the toxicologically equivalent trialkyl derivatives, formed from photolytic dissociation or ozonolysis in the atmosphere, may do so.

10.7.1.1 Gastrointestinal Absorption. Information on the rate of absorption of lead alkyls through the gastrointestinal tract is not available in the literature. Given the level of gastric acidity (pH 1.0) in humans, one would expect TML and TEL to be rapidly converted to the corresponding trialkyl forms, which are comparatively more stable (Bade and Huber, 1970). Given the similarity of the chemical and biochemical behavior of trialkyl leads to their Group IV analogs, the trialkyltins, the report of Barnes and Stoner (1958) that triethyltin is quantitatively absorbed from the GI tract indicates that triethyl and trimethyllead would be extensively absorbed via this route.

10.7.1.2 Percutaneous Absorption of Lead Alkyls. In contrast to inorganic lead salts, both TEL and TML are rapidly and extensively absorbed through the skin in rabbits and rats (Kehoe and Thamann, 1931; Laug and Kunze, 1948), and lethal effects can be rapidly induced in these animals by merely exposing the skin. Laug and Kunze (1948) observed that systemic uptake of TEL was still 6.5 percent even though most of the TEL was seen to have evaporated from the skin surface. The rate of passage of TML was somewhat slower than that of TEL in the study of Davis et al. (1963); absorption of either agent was retarded somewhat when applied in gasoline.

10.7.2 Biotransformation and Tissue Distribution of Lead Alkyls

In order to have an understanding of the *in vivo* fate of lead alkyls, it is useful to first discuss the biotransformation processes of lead alkyls known to occur in mammalian systems. Tetraethyl and tetramethyl lead both undergo oxidative dealkylation in mammals to the triethyl or trimethyl metabolites, which are now accepted as the actual toxic forms of these alkyls.

Studies of the biochemical mechanisms for these transformations, as noted by Kimmel et al. (1977), indicate a dealkylation mediated by a P-450 dependent mono-oxygenase system in liver microsomes, with intermediate hydroxylation. In addition to rats (Cremer, 1959; Stevens et al., 1960; Bolanowska, 1968), mice (Hayakawa, 1972), and rabbits (Bolanowska and Garczyński, 1968) this transformation also occurs in humans accidentally poisoned with TEL (Bolanowska et al., 1967) or workers chronically exposed to TEL (Adamiak-Ziemka and Bolanowska, 1970).

The rate of hepatic oxidative de-ethylation of TEL in mammals appears to be rather rapid; Cremer (1959) reported a maximum conversion rate of approximately 200 µg TEL/g rat liver/hour. In comparison with TEL, TML may undergo transformation at either a slower rate (in rats) or more rapidly (in mice), according to Cremer and Calloway (1961) and Hayakawa (1972).

Other transformation steps involve conversion of triethyl lead to diethyl form, the process appearing to be species-dependent. Bolanowska (1968) did not report the formation of diethyl lead in rats, while significant amounts of it are present in the urine of rabbits (Arai et al., 1981) and humans (Chiesura, 1970). Inorganic lead is formed in various species treated with tetraethyl lead, which may arise from degradation of the diethyl lead metabolite or some other direct process (Bolanowska, 1968). The latter process appears to occur in rats, as little or no diethyllead is found, whereas significant amounts of inorganic lead are present. Formation of inorganic lead with lead alkyl exposure may account for the hematological effects seen in humans chronically exposed to the lead alkyls (see Section 12.3), including children who inhale leaded gasoline vapor.

Partitioning of triethyl or trimethyl lead, the corresponding active metabolites of TEL and TML, between the erythrocyte and plasma appears to be species-dependent. Byington et al. (1980) studied the partitioning of triethyl lead between cells and plasma in vitro using washed human and rat erythrocytes and found that human cells had a very low affinity for the alkyl lead while rat cells bound the alkyl lead in the globin moiety at a ratio of three molecules per Hb tetramer. Similarly, it was found that injected triethyl lead was associated with whole blood levels approximately 10-fold greater than in rat plasma. The available literature on TEL poisoning in humans concurs, as significant plasma values of lead have been routinely reported (Boeckx et al., 1977; Golding and Stewart, 1982). These data indicate that the rat is a poor model to use in studying the adverse effects of lead alkyls in human subjects.

The biological half-time in blood for the lead alkyls depends on whether clearance of the tetraalkyl or trialkyl forms is being observed. Heard et al. (1979) found that ^{203}Pb-labeled TML and TEL inhaled by human volunteers was rapidly cleared from blood (by 10 hours), followed by a reappearance of lead. The fraction of lead in plasma initially was quite high, approximately 0.7, suggesting tetra/trialkyl lead; but the subsequent rise in blood lead showed all

of it essentially present in the cell, which would indicate inorganic or possibly diethyl lead. Triethyl lead in rabbits was more rapidly cleared from the blood of rabbits (3-5 days) than was the trimethyl form (15 days) when administered as such (Hayakawa, 1972).

Tissue distribution of lead in both humans and animals exposed to TEL and TML primarily involves the trialkyl metabolites. Levels are highest in liver, followed by kidney, then brain (Bolanowska et al., 1967; Grandjean and Nielsen, 1979). Nielsen et al. (1978) observed that measurable amounts of trialkyl lead were present in samples of brain tissue from subjects with no known occupational exposure.

The available studies on tissue retention of triethyl or trimethyl lead provide variable findings. Bolanowska (1968) noted that tissue levels of triethyl lead in rats were almost constant for 16 days after a single injection of TEL. Hayakawa (1972) found that the half-time of triethyl lead in brain was 7-8 days for rats; the half-time for trimethyl lead was much longer. In humans, Yamamura et al. (1975) reported two tissue compartments for triethyl lead having half-times of 35 and 100 days (Yamamura et al., 1975).

10.7.3 Excretion of Lead Alkyls

Excretion of lead through the renal tract is the main route of elimination in various species exposed to lead alkyls (Grandjean and Nielsen, 1979). The chemical forms of lead in urine suggest that the differing amounts of the various forms are species-dependent. Arai et al. (1981) found that rabbits given TEL parenterally excreted lead primarily in the form of diethyl lead (69 percent) and inorganic lead (27 percent), triethyl lead accounting only for 4 percent. In rats, Bolanowska and Garczynski (1968) found that levels of triethyl lead were somewhat higher in urine than was the case for rabbits. In humans, Chiesura (1970) found that trialkyl lead never was greater than 9 percent of total lead content in workers with heavy TEL exposure. Adamiak-Ziemka and Bolanowska (1970) reported similar data; the fraction of triethyl lead in the urine was approximately 10 percent of total lead.

The urinary rates of lead excretion in human subjects with known levels of TEL exposure were also reported by Adamiak-Ziemka and Bolanowska (1970). In workers involved with the blending and testing of leaded gasoline, workplace air levels of lead (as TEL) ranged from 0.037 to 0.289 mg Pb/m^3 and the corresponding urine levels ranged from 14 to 49 µg Pb/l, of which approximately 10 percent was triethyl lead.

10.8 SUMMARY

Toxicokinetic parameters of lead absorption, distribution, retention, and excretion connecting external environmental lead exposure to various adverse effects are discussed in this section. Also considered are various influences on these parameters, e.g., nutritional status, age, and stage of development.

A number of specific issues in lead metabolism by animals and humans merit special focus and these include:

1. How does the developing organism from gestation to maturity differ from the adult in toxicokinetic response to lead intake?
2. What do these differences in lead metabolism portend for relative risk for adverse effects?
3. What are the factors that significantly change the toxicokinetic parameters in ways relevant to assessing health risk?
4. How do the various interrelationships among body compartments for lead translate to assessment of internal exposure and changes in internal exposure?

10.8.1 Lead Absorption in Humans and Animals

The amounts of lead entering the bloodstream via various routes of absorption are influenced not only by the levels of the element in a given medium but also by various physical and chemical parameters and specific host factors, such as age and nutritional status.

10.8.1.1 Respiratory Absorption of Lead. The movement of lead from ambient air to the bloodstream is a two-part process: deposition of some fraction of inhaled air lead in the deeper part of the respiratory tract and absorption of the deposited fraction. For adult humans, the deposition rate of particulate airborne lead as likely encountered by the general population is around 30-50 percent, with these rates being modified by such factors as particle size and ventilation rates. It also appears that essentially all of the lead deposited in the lower respiratory tract is absorbed, so that the overall absorption rate is governed by the deposition rate, i.e., approximately 30-50 percent. Autopsy results showing no lead accumulation in the lung indicate quantitative absorption of deposited lead.

All of the available data for lead uptake via the respiratory tract in humans have been obtained with adults. Respiratory uptake of lead in children, while not fully quantifiable, appears to be comparatively greater on a body weight basis, compared to adults. A second factor influencing the relative deposition rate in children has to do with airway dimensions. One report has estimated that the 10-year-old child has a deposition rate 1.6- to 2.7-fold higher than the adult on a weight basis.

It appears that the chemical form of the lead compound inhaled is not a major determinant of the extent of alveolar absorption of lead. While experimental animal data for quantitative assessment of lead deposition and absorption for the lung and upper respiratory tract are

limited, available information from the rat, rabbit, dog, and nonhuman primate support the findings that respired lead in humans is extensively and rapidly absorbed.

10.8.1.2 Gastrointestinal Absorption of Lead. Gastrointestinal absorption of lead mainly involves lead uptake from food and beverages as well as lead deposited in the upper respiratory tract which is eventually swallowed. It also includes ingestion of non-food material, primarily in children via normal mouthing activity and pica. Two issues of concern with lead uptake from the gut are the comparative rates of such absorption in developing vs. adult organisms, including humans, and how the relative bioavailability of lead affects such uptake.

By use of metabolic balance and isotopic (radioisotope or stable isotope) studies, various laboratories have provided estimates of lead absorption in the human adult on the order of 10-15 percent. This rate can be significantly increased under fasting conditions to 45 percent, compared to lead ingested with food. The latter figure also suggests that beverage lead is absorbed to a greater degree since much beverage ingestion occurs between meals.

The relationship of the chemical/biochemical form of lead in the gut to absorption rate has been studied, although interpretation is complicated by the relatively small amounts given and the presence of various components in food already present in the gut. In general, however, chemical forms of lead or their incorporation into biological matrices seems to have a minimal impact on lead absorption in the human gut. Several studies have focused on the question of differences in gastrointestinal absorption rates for lead between children and adults. It would appear that such rates for children are considerably higher than for adults: 10-15 percent for adults vs. approximately 50 percent for children. Available data for the absorption of lead from non-food items such as dust and dirt on hands are limited, but one study has estimated a figure of 30 percent. For paint chips, a value of about 17 percent has been estimated.

Experimental animal studies show that, like humans, the adult absorbs much less lead from the gut than the developing animal. Adult rats maintained on ordinary rat chow absorb 1 percent or less of the dietary lead. Various animal species studies make it clear that the newborn absorbs a much greater amount of lead than the adult, supporting studies showing this age dependency in humans. Compared to an absorption rate of about 1 percent in adult rats, the rat pup has a rate 40-50 times greater. Part, but not most, of the difference can be ascribed to a difference in dietary composition. In nonhuman primates, infant monkeys absorb 65-85 percent of lead from the gut, compared to 4 percent for the adults.

The bioavailability of lead in the gastrointestinal (GI) tract as a factor in its absorption has been the focus of a number of experimental studies. These data show that: 1) lead in a number of forms is absorbed about equally, except for the sulfide; 2) lead in dirt and dust and as different chemical forms is absorbed at about the same rate as pure lead salts

added to diet; 3) lead in paint chips undergoes significant uptake from the gut; and 4) in some cases, physical size of particulate lead can affect the rate of GI absorption.

10.8.1.3 Percutaneous Absorption of Lead. Absorption of inorganic lead compounds through the skin is of much less significance than through the respiratory and gastrointestinal routes. This is in contrast to the case with lead alkyls (See Section 1.10.6). One recent study using human volunteers and ^{203}Pb-labeled lead acetate showed that under normal conditions, absorption approaches 0.06 percent.

10.8.1.4 Transplacental Transfer of Lead. Lead uptake by the human and animal fetus readily occurs, such transfer going on by the 12th week of gestation in humans, with increasing fetal uptake throughout development. Cord blood contains significant amounts of lead, correlating with but somewhat lower than maternal blood lead levels. Evidence for such transfer, besides lead content of cord blood, includes fetal tissue analyses and reduction in maternal blood lead during pregnancy. There also appears to be a seasonal effect on the fetus, summer-born children showing a trend to higher blood lead levels than those born in the spring.

10.8.2 Distribution of Lead in Humans and Animals

In this subsection, the distributional characteristics of lead in various portions of the body--blood, soft tissue, calcified tissue, and the "chelatable" or potentially toxic body burden--are discussed as a function of such variables as exposure history and age.

10.8.2.1 Lead in Blood. More than 99 percent of blood lead is associated with the erythrocyte in humans under steady-state conditions, but it is the very small fraction transported in plasma and extracellular fluid that provides lead to the various body organs. Most (~50 percent) of erythrocyte lead is bound within the cell, primarily associated with hemoglobin (particularly HbA_2), with approximately 5 percent bound to a 10,000-dalton fraction, 20 percent to a heavier molecule, and 25 percent to lower weight species.

Whole blood lead in daily equilibrium with other compartments in adult humans appears to have a biological half-time of 25-28 days and comprises about 1.9 mg in total lead content. Human blood lead responds rather quickly to abrupt changes in exposure. With increased lead intake, blood lead achieves a new value in approximately 40-60 days, while a decrease in exposure may be associated with variable new blood values, depending upon the exposure history. This dependence presumably reflects lead resorption from bone. With age, furthermore, there appears to be little change in blood lead during adulthood. Levels of lead in blood of children tend to show a peaking trend at 2-3 years of age, probably due to mouthing activity, followed by a decline. In older children and adults, levels of lead are sex-related, females showing lower levels than men even at comparable levels of exposure.

In plasma, lead is virtually all bound to albumin and only trace amounts to high weight globulins. It is not possible to state which binding form constitutes an "active" fraction for movement to tissues. The most recent studies of the erythrocyte-plasma relationship in humans indicate that there is an equilibrium between these blood compartments, such that levels in plasma rise with levels in whole blood.

10.8.2.2 Lead Levels in Tissues. Of necessity, various relationships of tissue lead to exposure and toxicity in humans must generally be obtained from autopsy samples. Limitations on such data include questions of how samples represent lead behavior in the living population, particularly with reference to prolonged illness and disease states. The adequate characterization of exposure for victims of fatal accidents is a problem, as is the fact that such studies are cross-sectional in nature, with different age groups assumed to have had similar exposure in the past.

10.8.2.2.1 Soft tissues. After age 20, most soft tissues in humans do not show age-related changes, in contrast to bone. Kidney cortex shows increase in lead with age which may be associated with formation of nuclear inclusion bodies. Absence of lead accumulation in most soft tissues is due to a turnover rate for lead which is similar to that in blood.

Based on several autopsy studies, it appears that soft tissue lead content for individuals not occupationally exposed is generally below 0.5 μg/g wet weight, with higher values for aorta and kidney cortex. Brain tissue lead level is generally below 0.2 ppm wet weight with no change with increasing age, although the cross-sectional nature of these data would make changes in low brain lead levels difficult to discern. Autopsy data for both children and adults indicate that lead is selectively accumulated in the hippocampus, a finding that is also consistent with the reginal distribution in experimental animals.

Comparisons of lead levels in soft tissue autopsy samples from children with results from adults indicate that such values are lower in infants than in older children, while children aged 1-16 years had levels comparable to adult women. In one study, lead content of brain regions did not materially differ for infants and older children compared to adults. Complicating these data somewhat are changes in tissue mass with age, although such changes are less than for the skeletal system.

Subcellular distribution of lead in soft tissue is not uniform, with high amounts of lead being sequestered in the mitochondria and nucleus. Nuclear accumulation is consistent with the existence of lead-containing nuclear inclusions in various species and a large body of data demonstrating the sensitivity of mitochondria to injury by lead.

10.8.2.2.2 Mineralizing tissue. Lead becomes localized and accumulates in human calcified tissues, i.e., bones and teeth. This accumulation in humans begins with fetal development and continues to approximately 60 years of age. The extent of lead accumulation in bone ranges up

to 200 mg in men ages 60-70 years, while in women lower values have been measured. Based upon various studies, approximately 95 percent of total body lead is lodged in the bones of human adults, with uptake distributed over trabecular and compact bone. In the human adult, bone lead is both the most inert and largest body pool, and accumulation can serve to maintain elevated blood lead levels years after exposure, particularly occupational exposure, has ended.

Compared to the human adult, 73 percent of body lead is lodged in the bones of children, which is consistent with other information that the skeletal system of children is more metabolically active than in the adult. While the increase in bone lead across childhood is modest, about 2-fold if expressed as concentration, the total accumulation rate is actually 80-fold, taking into account a 40-fold increase in skeletal mass. To the extent that some significant fraction of total bone lead in children and adults is relatively labile, it is more appropriate in terms of health risk for the whole organism to consider the total accumulation rather than just changes in concentration.

The traditional view that the skeletal system was a "total" sink for body lead (and by implication a biological safety feature to permit significant exposure in industrialized populations) never did accord with even older information on bone physiology, e.g., bone remodelling, and is now giving way to the view that there are at least several bone compartments for lead, with different mobility profiles. It would appear, then, that "bone lead" may be more of an insidious source of long-term internal exposure than a sink for the element. This aspect of the issue is summarized more fully in the next section. Available information from studies of such subjects as uranium miners and human volunteers ingesting stable isotopes indicates that there is a relatively inert bone compartment for lead, having a half-time of several decades, and a rather labile compartment which permits an equilibrium between bone and tissue lead.

Tooth lead also increases with age at a rate proportional to exposure and roughly proportional to blood lead in humans and experimental animals. Dentine lead is perhaps the most responsive component of teeth to lead exposure since it is laid down from the time of eruption until shedding. It is this characteristic which underlies the utility of dentine lead levels in assessing long-term exposure.

10.8.2.2.3 Chelatable lead. Mobile lead in organs and systems is potentially more active toxicologically in terms of being available to biological sites of action. Hence, this fraction of total body lead burden is a more significant predictor of imminent toxicity. In reality, direct measurement of such a fraction in human subjects would not be possible. In this regard, "chelatable" lead, measured as the extent of plumburesis in response to administration of a chelating agent, is not viewed as the most useful probe of undue body burden in children and adults.

A quantitative description of the inputs to the body lead fraction that is chelant-mobilizable is difficult to fully define, but it most likely includes a labile lead compartment within bone as well as in soft tissues. Support for this view includes: 1) the age dependency of chelatable lead, but not lead in blood or soft tissues; 2) evidence of removal of bone lead in chelation studies with experimental animals; 3) in vitro studies of lead mobilization in bone organ explants under closely defined conditions; 4) tracer modelling estimates in human subjects; and 5) the complex nonlinear relationship of blood lead and lead intake through various media. Data for children and adults showing a logarithmic relationship of chelatable lead to blood lead and the phenomenon of "rebound" in blood lead elevation after chelation therapy regimens (without obvious external re-exposure) offer further support.

10.8.2.2.4 Animal studies. Animal studies have been of help in sorting out some of the relationships of lead exposure to in vivo distribution of the element, particularly the impact of skeletal lead on whole body retention. In rats, lead administration results in an initial increase in soft tissues, followed by loss from soft tissue via excretion and transfer to bone. Lead distribution appears to be relatively independent of dose. Other studies have shown that lead loss from organs follows first-order kinetics except for bone, and the skeletal system in rats and mice is the kinetically rate-limiting step in whole-body lead clearance.

The neonatal animal seems to retain proportionally higher levels of tissue lead compared to the adult and manifests slow decay of brain lead levels while showing a significant decline over time in other tissues. This appears to be the result of enhanced lead entry to the brain because of a poorly developed brain barrier system as well as enhanced body retention of lead by young animals.

The effects of such changes as metabolic stress and nutritional status on body redistribution of lead have been noted. Lactating mice, for example, are known to demonstrate tissue redistribution of lead, specifically bone lead resorption with subsequent transfer of both lead and calcium from mother to pups.

10.8.3 Lead Excretion and Retention in Humans and Animals

10.8.3.1 Human Studies. Dietary lead in humans and animals that is not absorbed passes through the gastrointestinal tract and is eliminated with feces, as is the fraction of air lead that is swallowed and not absorbed. Lead entering the bloodstream and not retained is excreted through the renal and GI tracts, the latter via biliary clearance. The amounts excreted through these routes are a function of such factors as species, age, and exposure characteristics.

Based upon the human metabolic balance data and isotope excretion findings of various investigators, it appears that short-term lead excretion in adult humans amounts to 50-60 percent of the absorbed fraction, with the balance moving primarily to bone and some fraction (approximately half) of this stored amount eventually being excreted. This overall retention figure of 25 percent necessarily assumes that isotope clearance reflects that for body lead in all compartments. The rapidly excreted fraction has a biological half-time of 20-25 days, similar to that for lead removal from blood. This similarity indicates a steady rate of lead clearance from the body. In terms of partitioning of excreted lead between urine and bile, one study indicates that the biliary clearance is about 50 percent that of renal clearance.

Lead is accumulated in the human body with age, mainly in bone, up to around 60 years of age, when a decrease occurs with changes in intake as well as in bone mineral metabolism. As noted earlier, the total amount of lead in long-term retention can approach 200 mg, and even much higher in the case of occupational exposure. This corresponds to a lifetime average retention rate of 9-10 μg Pg/day. Within shorter time frames, however, retention will vary considerably due to such factors as development, disruption in the individuals' equilibrium with lead intake, and the onset of such states as osteoporosis.

The age dependency of lead retention/excretion in humans has not been well studied, but most of the available information indicates that children, particularly infants, retain a significantly higher amount of lead. While autopsy data indicate that pediatric subjects at isolated points in time actually have a lower fraction of body lead lodged in bone, a full understanding of longer-term retention over childhood must consider the exponential growth rate occurring in a child's skeletal system over the time period for which bone lead concentrations have been gathered. This parameter itself represents a 40-fold mass increase. This significant skeletal growth rate has an impact on an obvious question: if children take in more lead on a body weight basis than adults, absorb and retain more lead than adults, and show only modest elevations in blood lead compared to adults in the face of a more active skeletal system, where does the lead go? A second factor is the assumption that blood lead in children relates to body lead burden in the same quantitative fashion as in adults, an assumption that remains to be adequately proven.

10.8.3.2 Animal Studies. In rats and other experimental animals, both urinary and fecal excretion appear to be important routes of lead removal from the organism; the relative partitioning between the two modes is species- and dose-dependent. With regard to species differences, biliary clearance of lead in the dog is but 2 percent of that for the rat, while such excretion in the rabbit is 50 percent that of the rat.

Lead movement from laboratory animals to their offspring via milk constituents is a route of excretion for the mother as well as an exposure route for the young. Comparative studies

of lead retention in developing vs. adult animals, e.g., rats, mice, and non-human primates, make it clear that retention is significantly greater in the young animal. These observations support those studies showing greater lead retention in children. Some recent data indicate that a differential retention of lead in young rats persists into the post-weaning period, calculated as either uniform dosing or uniform exposure.

10.8.4 Interactions of Lead with Essential Metals and Other Factors

Toxic elements such as lead are affected in their toxicokinetic or toxicological behavior by interactions with a variety of biochemical factors such as nutrients.

10.8.4.1 Human Studies. In humans the interactive behavior of lead and various nutritional factors is expressed most significantly in young children, with such interactions occurring against a backdrop of rather widespread deficiencies in a number of nutritional components. Various surveys have indicated that deficiency in iron, calcium, zinc, and vitamins are widespread among the pediatric population, particularly the poor. A number of reports have documented the association of lead absorption with suboptimal nutritional states for iron and calcium, reduced intake being associated with increased lead absorption.

10.8.4.2 Animal Studies. Reports of lead-nutrient interactions in experimental animals have generally described such relationships for a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the recent data are for calcium, iron, phosphorus, and vitamin D. Many studies have established that diminished dietary calcium is associated with increased blood and soft tissue lead content in such diverse species as the rat, pig, horse, sheep, and domestic fowl. The increased body burden of lead arises from both increased GI absorption and increased retention, indicating that the lead-calcium interaction operates at both the gut wall and within body compartments. Lead appears to traverse the gut via both passive and active transfer, involves transport proteins normally operating for calcium transport, and is taken up at the site of phosphorus, not calcium, absorption.

Iron deficiency is associated with an increase in lead of tissues and increased toxicity, an effect which is expressed at the level of lead uptake by the gut wall. In vitro studies indicate an interaction through receptor binding competition at a common site. This probably involves iron-binding proteins. Similarly, dietary phosphate deficiency enhances the extent of lead retention and toxicity via increased uptake of lead at the gut wall, both lead and phosphate being absorbed at the same site in the small intestine. Results of various studies of the resorption of phosphate along with lead as one further mechanism of elevation of tissue lead have not been conclusive. Since calcium plus phosphate retards lead absorption to a greater degree than simply the sums of the interactions, it has been postulated that an insoluble complex of all these elements may be the basis of this retardation.

Unlike the inverse relationship existing for calcium, iron, and phosphate vs. lead uptake, vitamin D levels appear to be directly related to the rate of lead absorption from the GI tract, since the vitamin stimulates the same region of the duodenum where lead is absorbed. A number of other nutrient factors are known to have an interactive relationship with lead:

1. Increases in dietary lipids increase the extent of lead absorption, with the extent of the increase being highest with polyunsaturates and lowest with saturated fats, e.g., tristearin.
2. The interactive relationship of lead and dietary protein is not clearcut, and either suboptimal or excess protein intake will increase lead absorption.
3. Certain milk components, particularly lactose, will greatly enhance lead absorption in the nursing animal.
4. Zinc deficiency promotes lead absorption as does reduced dietary copper.

10.8.5 Interrelationships of Lead Exposure with Exposure Indicators and Tissue Lead Burdens

There are three issues involving lead toxicokinetics which evolve toward a full connection between lead exposure and its adverse effects: 1) the temporal characteristics of internal indices of lead exposure; 2) the biological aspects of the relationship of lead in various media to various indicators in internal exposure; and 3) the relationship of various internal indicators of exposure to target tissue lead burdens.

10.8.5.1 Temporal Characteristics of Internal Indicators of Lead Exposure. The biological half-time for newly absorbed lead in blood appears to be of the order of weeks or several months, so that this medium reflects relatively recent exposure. If recent exposure is fairly representative of exposure over a considerable period of time, e.g., exposure of lead workers, then blood lead is more useful than for cases where exposure is intermittent or different across time, as in the case of lead exposure of children. Accessible mineralized tissue, such as shed teeth, extend the time frame back to years of exposure, since teeth accumulate lead with age and as a function of the extent of exposure. Such measurements are, however, retrospective in nature, in that identification of excessive exposure occurs after the fact and thus limits the possibility of timely medical intervention, exposure abatement, or regulatory policy concerned with ongoing control strategies.

Perhaps the most practical solution to the dilemma posed by both tooth and blood lead analyses is *in situ* measurement of lead in teeth or bone during the time when active accumulation occurs, e.g., 2-3-year-old children. Available data using X-ray fluorescence analysis do suggest that such approaches are feasible and can be reconciled with such issues as acceptable radiation hazard risk to subjects.

10.8.5.2 Biological Aspects of External Exposure-Internal Indicator Relationships. It is clear from a reading of the literature that the relationship of lead in relevant media for human exposure to blood lead is curvilinear when viewed over a relatively broad range of blood

lead values. This implies that the unit change in blood lead per unit intake of lead in some medium varies across this range of exposure, with comparatively smaller blood lead changes as internal exposure increases.

Given our present knowledge, such a relationship cannot be taken to mean that body uptake of lead is proportionately lower at higher exposure, for it may simply mean that blood lead becomes an increasingly unreliable measure of target tissue lead burden with increasing exposure. While the basis of the curvilinear relationship remains to be identified, available animal data suggest that it does not reflect exposure-dependent absorption or excretion rates.

10.8.5.3 Internal Indicator-Tissue Lead Relationships. In living human subjects, it is not possible to directly determine tissue lead burdens or how these relate to adverse effects in target tissues; some accessible indicator, e.g., lead in a medium such as blood or a biochemical surrogate of lead such as EP, must be employed. While blood lead still remains the only practical measure of excessive lead exposure and health risk, evidence continues to accumulate that such an index has limitations in either reflecting tissue lead burdens or changes in such tissues with changes in exposure.

At present, the measurement of plumburesis associated with challenge by a single dose of a lead chelating agent such as $CaNa_2EDTA$ is considered the best indicator of the mobile, potentially toxic fraction of body lead. Chelatable lead is logarithmically related to blood lead, such that incremental increase in blood lead is associated with an increasingly larger increment of mobilizable lead. The problems associated with this logarithmic relationship may be seen in studies of children and lead workers in whom moderate elevation in blood lead can disguise levels of mobile body lead. This reduces the margin of protection against severe intoxication. The biological basis of the logarithmic chelatable lead-blood lead relationship rests, in large measure, with the existence of a sizable bone lead compartment that is mobile enough to undergo chelation removal and, hence, potentially mobile enough to move into target tissues.

Studies of the relative mobility of chelatable lead over time indicate that, in former lead workers, removal from exposure leads to a protracted washing out of lead (from bone resorption of lead) to blood and tissues, with preservation of a bone burden amenable to subsequent chelation. Studies with children are inconclusive, since the one investigation directed to this end employed pediatric subjects who all underwent chelation therapy during periods of severe lead poisoning. Animal studies demonstrate that changes in blood lead with increasing exposure do not agree with tissue uptake in a time-concordant fasion, nor does decrease in blood lead with reduced exposure signal a similar decrease in target tissue, particularly in the brain of the developing organism.

10.8.6 Metabolism of Lead Alkyls

The lower alkyl lead components used as gasoline additives, tetraethyl lead (TEL) and tetramethyl lead (TML), may themselves poise a toxic risk to humans. In particular, there is among children a problem of sniffing leaded gasoline.

10.8.6.1 Absorption of Lead Alkyls in Humans and Animals. Human volunteers inhaling labeled TEL and TML show lung deposition rates for the lead alkyls of 37 and 51 percent, respectively, values which are similar to those for particulate inorganic lead. Significant portions of these deposited amounts were eventually absorbed. Respiratory absorption of organolead bound to particulate matter has not been specifically studied as such.

While specific data for the GI absorption of lead alkyls in humans and animals are not available, their close similarity to organotin compounds, which are quantitatively absorbed, would argue for extensive GI absorption. In contrast to inorganic lead salts, the lower lead alkyls are extensively absorbed through the skin and animal data show lethal effects with percutaneous uptake as the sole route of exposure.

10.8.6.2 Biotransformation and Tissue Distribution of Lead Alkyls. The lower lead alkyls TEL and TML undergo monodealkylation in the liver of mammalian species via the P-450-dependent mono-oxygenase enzyme system. Such transformation is very rapid. Further transformation involves conversion to the dialkyl and inorganic lead forms, the latter accounting for the effects on heme biosynthesis and erythropoiesis observed in alkyl lead intoxication. Alykl lead is rapidly cleared from blood, shows a higher partitioning into plasma than inorganic lead with triethyl lead clearance being more rapid than the methyl analog.

Tissue distribution of alkyl lead in humans and animals primarily involves the trialkyl metabolites. Levels are highest in liver, followed by kidney, then brain. Of interest is the fact that there are detectable amounts of trialkyl lead from autopsy samples of human brain even in the absence of occupational exposure. In humans, there appear to be two tissue compartments for triethyl lead, having half-times of 35 and 100 days.

10.8.6.3 Excretion of Lead Alkyls. With alkyl lead exposure, excretion of lead through the renal tract is the main route of elimination. The chemical forms being excreted appear to be species-dependent. In humans, trialkyl lead in workers chronically exposed to alkyl lead is a minor component of urine lead, approximately 9 percent.

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11. ASSESSMENT OF LEAD EXPOSURES AND ABSORPTION IN HUMAN POPULATIONS

11.1 INTRODUCTION

The purpose of this chapter is to describe effects on internal body burdens of lead in human populations resulting from exposure to lead in their environment. This chapter discusses changes in various internal exposure indices that follow changes in external lead exposures. The main index of internal lead exposure focused on herein is blood lead levels, although other indices, such as levels of lead in teeth and bone are also briefly discussed. As noted in Chapter 10, blood lead levels most closely reflect recent exposures to environmental lead. On the other hand, teeth and bone lead levels better reflect or index cumulative exposures.

The following terms and definitions will be used in this chapter. Sources of lead are those components of the environment (e.g., gasoline combustion, smelters) from which significant quantities of lead are released into various environmental media of exposure. Environmental media are direct routes by which humans become exposed to lead (e.g., air, soil, water, dust). External exposures are levels at which lead is present in any or all of the environmental media. Internal exposures are the amounts of lead present at various sites within the body.

The present chapter is organizationally structured so as to achieve the following four main objectives:

(1) Elucidation of patterns of absorbed lead in U.S. populations and identification of important demographic covariates.

(2) Characterization of relationships between external and internal exposures by exposure medium (air, food, water or dust).

(3) Identification of specific sources of lead which result in increased internal exposure levels.

(4) Estimation of the relative contributions of various sources of lead in the environment to total internal exposure.

The existing scientific literature must be examined in light of the investigators' own objectives and the quality of the scientific investigations performed. Although all studies need to be evaluated in regard to their methodology, the more quantitative studies are evaluated here in greater depth. A discussion of the main types of methodological points considered in such evaluations is presented in Section 11.2.

After discussing methodological aspects, patterns of internal exposure to lead in human populations are delineated in Section 11.3. This begins with a brief examination of the

historical record of internal lead exposure in human populations. These data serve as a backdrop against which recent U.S. levels can be contrasted and defines the relative magnitude of external lead exposures in the past and present. The contrast is structured as follows: historical data, recent data from populations thought to be isolated from urbanized cultures, and then U.S. populations showing various degrees of urbanization and industrialization.

Recent patterns of internal exposure in U.S. populations are discussed in greater detail. Estimates of internal lead exposure and identification of demographic covariates are made. Studies examining the recent past for evidence of change in levels in internal exposure are presented. A discussion follows regarding exposure covariates of blood lead levels in urban U.S. children, who are at special risk for increased internal exposure.

The statistical treatment of distributions of blood lead levels in human populations is the next topic discussed. As part of that discussion, the empirical characteristics of blood lead distributions in well defined homogeneous populations are denoted. Important issues addressed include the proper choice of estimators of central tendency and dispersion, estimators of percentile values and the potential influence of errors in measurement on statistical estimation involving blood lead data.

Section 11.4 focuses on general relationships between external exposures and levels of internal exposure. The distribution of lead in man is diagramatically depicted by the component model shown in Figure 1. Of particular importance for this document is the relationship between lead in air and lead in blood. If lead in air were the only medium of exposure, then the interpretation of a statistical relationship between lead in air and lead in blood would be relatively simple. However, this is not the case. Lead is present in a number of environmental media, as described in Chapter 7 and summarized in Figure 11-1. There are relationships between lead levels in air and lead concentrations in food, soil, dust and water. As shown in Chapters 6, 7 and 8, lead emitted into the atmosphere ultimately comes back to contaminate the earth. However, only limited data are currently available that provide a quantitative estimate of the magnitude of this secondary lead exposure. The implication is that an analysis involving estimated lead levels in all environmental media may produce an underestimate of the relationship between lead in blood and lead in air.

The discussion of relationships between external exposure and internal absorption commences with air lead exposures. Both experimental and epidemiological studies are discussed. Several studies are identified as being of most importance in determining the quantitative relationship between lead in blood and lead in air. The shape of the relationship between blood lead and air lead is of particular interest and importance.

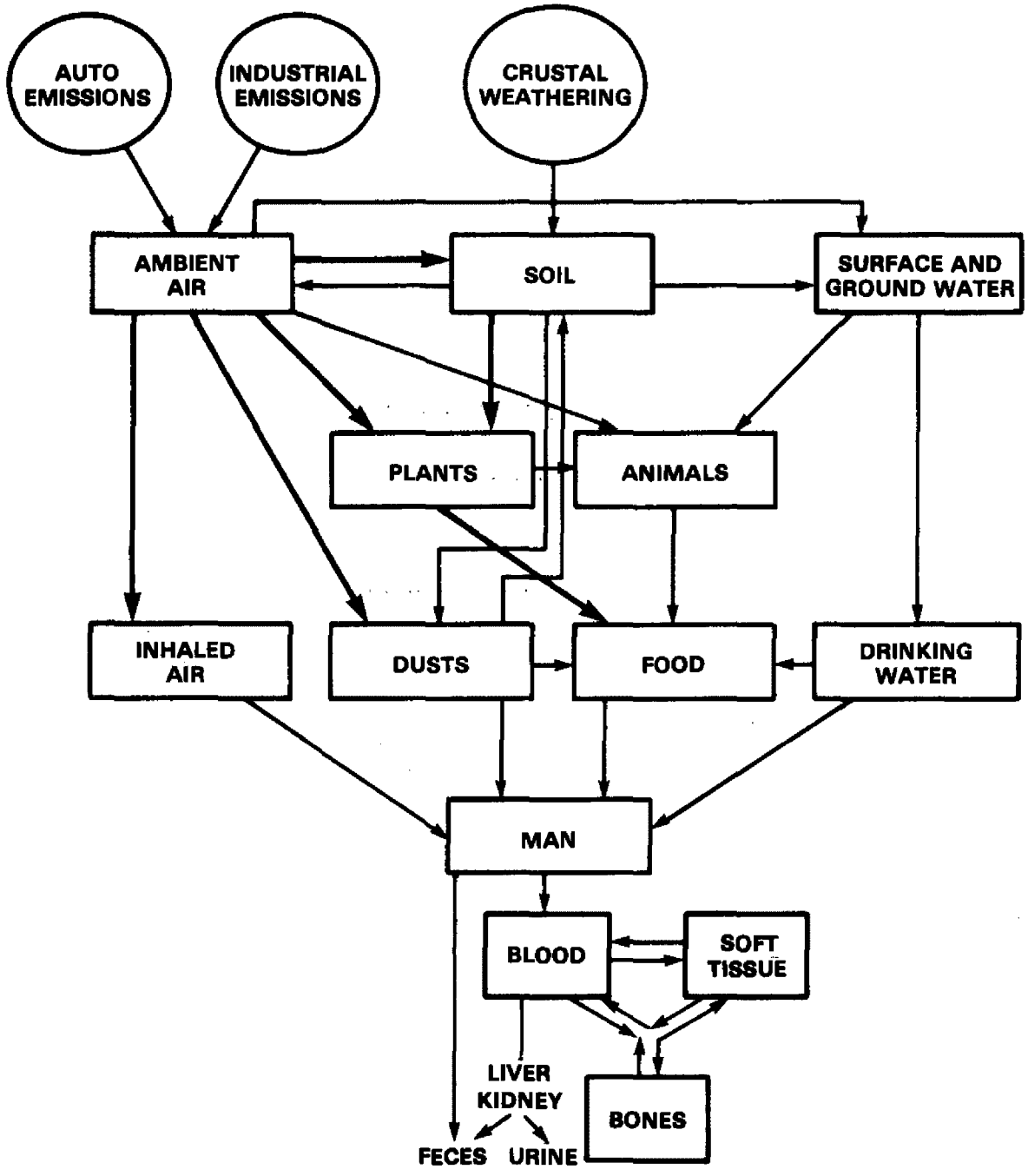

Figure 11-1. Pathways of lead from the environment to man.

After discussion of air lead vs. blood lead relationships, the chapter next discusses the relationship of blood lead to atmospheric lead found in other environmental media. Section 11.5 describes studies of specific lead exposure situations useful in identifying specific environmental sources of lead that contribute to elevated body burdens of lead. The chapter concludes with a summary of key information and conclusions derived from the scientific evidence reviewed.

11.2 METHODOLOGICAL CONSIDERATIONS

11.2.1 Analytical Problems

Internal lead exposure levels in human populations have been estimated by analyses of a variety of biological tissue matrices (e.g., blood, teeth, bone, and hair). Lead levels in each of these matrices have particular biological meanings with regard to external exposure status; these relationships are discussed in Chapter 10. The principal internal exposure index discussed in this chapter is blood lead concentration. Blood lead concentrations are most reflective of recent exposure to lead and bear a consistent relationship to levels of lead in the external environment if the latter have been stable. Blood lead levels are variously reported as µg/100 g, µg/100 ml, µg/dl, ppm, ppb, and µm/l. The first four measures are roughly equivalent, whereas ppb values are simply divisible by 1000 to be equivalent. Actually there is a small but not meaningful difference in blood lead levels reported on a per volume vs. per weight difference. The difference results from the density of blood being slightly greater than 1 g/ml. For the purposes of this chapter, data reported on a weight or volume basis are considered equal. On the other hand, blood lead data reported on a µmol/l basis must be multiplied by 20.72 to get the equivalent µg/dl value. Data reported originally as µmol/l in studies reviewed here are converted to µg/dl in subsequent sections of this chapter.

As discussed in Chapter 9, the measurement of lead in blood has been accomplished via a succession of analytical procedures over the years. The first reliable analytical methods available were wet chemistry procedures that have been succeeded by increasingly automated instrumental procedures. With these changes in technology there has been increasing recognition of the importance of controlling for contamination in the sampling and analytical procedures. These advances, as well as institution of external quality control programs, have resulted in markedly improved analytical results. Data summarized in Chapter 9 show that a generalized improvement in analytical results across many laboratories occurred during Federal Fiscal Years 1977 to 1979. No futher marked improvement was seen during Federal Fiscal Years 1979 to 1981.

As difficult as getting accurate blood lead determinations is, the achievement of accurate lead isotopic determinations is even more difficult. Experience gained from the isotopic

lead experiment (ILE) in Italy (reviewed in detail in Section 11.5.1.1.1) has indicated that extremely aggressive quality control and contamination control programs must be implemented to achieve acceptable results. With proper procedures, meaningful differences on the order of a single nanogram are achievable.

11.2.2 Statistical Approaches

Many studies summarize the distribution of lead levels in humans. These studies usually report measures of central tendency (means) and dispersion (variances). In this chapter, the term "mean" refers to the arithmetic mean unless stated otherwise. This measure is always an estimate of the average value, but it estimates the center of the distribution (50th percentile) only for symmetric distributions. Many authors provide geometric means, which estimate the center of the distribution if the distribution is lognormal. Geometric means are influenced less by unusually large values than are arithmetic means. A complete discussion of the lognormal distribution is given by Aitchison and Brown (1966), including formulas for converting from arithmetic to geometric means.

Most studies also give sample variances or standard deviations in addition to the means. If geometric means are given, then the corresponding measure of dispersion is the geometric standard deviation. Aitchison and Brown (1966) give formulas for the geometric standard deviation and, also, explain how to estimate percentiles and construct confidence intervals. All of the measures of dispersion actually include three sources of variation: population variation, measurement variation and variation due to sampling error. Values for these components are needed in order to evaluate a study correctly.

A separate issue is the form of the distribution of blood lead values. Although the normal and lognormal distributions are commonly used, there are many other possible distributions. The form is important for two reasons: 1) it determines which is more appropriate, the arithmetic or geometric mean, and 2) it determines estimates of the fraction of a population exceeding given internal lead levels under various external exposures. Both of these questions arise in the discussion of the distribution of human blood lead levels.

Many studies attempt to relate blood lead levels to an estimate of dose such as lead levels in air. Standard regression techniques should be used with caution, since they assume that the dose variable is measured without error. The dose variable is an estimate of the actual lead intake and has inherent inaccuracies. As a result, the slopes tend to be underestimated; however, it is extremely difficult to quantify the actual amount of this bias. Multiple regression analyses have additional problems. Many of the covariates that measure external exposures are highly correlated with each other. For example, much of the soil lead and house dust lead comes from the air. The exact effect of such high correlations with each other on the regression coefficients is not clear.

11.3 LEAD IN HUMAN POPULATIONS

11.3.1 Introduction

This section is designed to provide insight into current levels of lead absorption in the U.S. and other countries, and how they differ from "natural" levels, to examine the influence of demographic factors, and to describe the degree of internal exposure in selected population subgroups. This section will also examine time trend studies of blood lead levels.

11.3.2 Ancient and Remote Populations

A question of major interest in understanding environmental pollutants is the extent to which current ambient exposures exceed background levels. Because lead is a naturally occurring element it can be surmised that some level has been and will always be present in the human body; the question of interest is what is the difference in the levels of current subgroups of the United States population from those "natural" levels. Information regarding this issue has been developed from studies of populations that lived in the past and populations that currently live in remote areas far from the influence of industrial and urban lead exposures.

Man has used lead since antiquity for a variety of purposes. These uses have afforded the opportunity for some segments of the human population to be exposed to lead and subsequently absorb it into the body. Because lead accumulates over a lifetime in bones and teeth and because bones and teeth stay intact for extremely long times, it is possible to estimate the extent to which populations in the past have been exposed to lead.

Because of the problems of scarcity of samples and little knowledge of how representative the samples are of conditions at the time, the data from these studies provide only rough estimates of the extent of absorption. Further complicating the interpretation of these data are debates over proper analytical procedures and the question of whether skeletons and teeth pick up or release lead from or to the soil in which they are interred.

Despite these difficulties, several studies provide data by which to estimate internal exposure patterns among ancient populations, and some studies have included data from both past and current populations for comparisons. Figure 11-2, which is adapted from Angle (1982) displays a historical view of the estimated lead usage and data from ancient bone and teeth lead levels. There is a reasonably good fit. There appears to be an increase in both lead usage and absorption over the time span covered. Specifics of these studies of bone and teeth will be presented in Section 11.3.2.1. In contrast to the study of ancient populations using bone and teeth lead levels, several studies have looked at the issue of lead contamination from the perspective of comparing current remote and urbanized populations. These studies have used blood lead levels as an indicator and found mean blood concentrations in remote

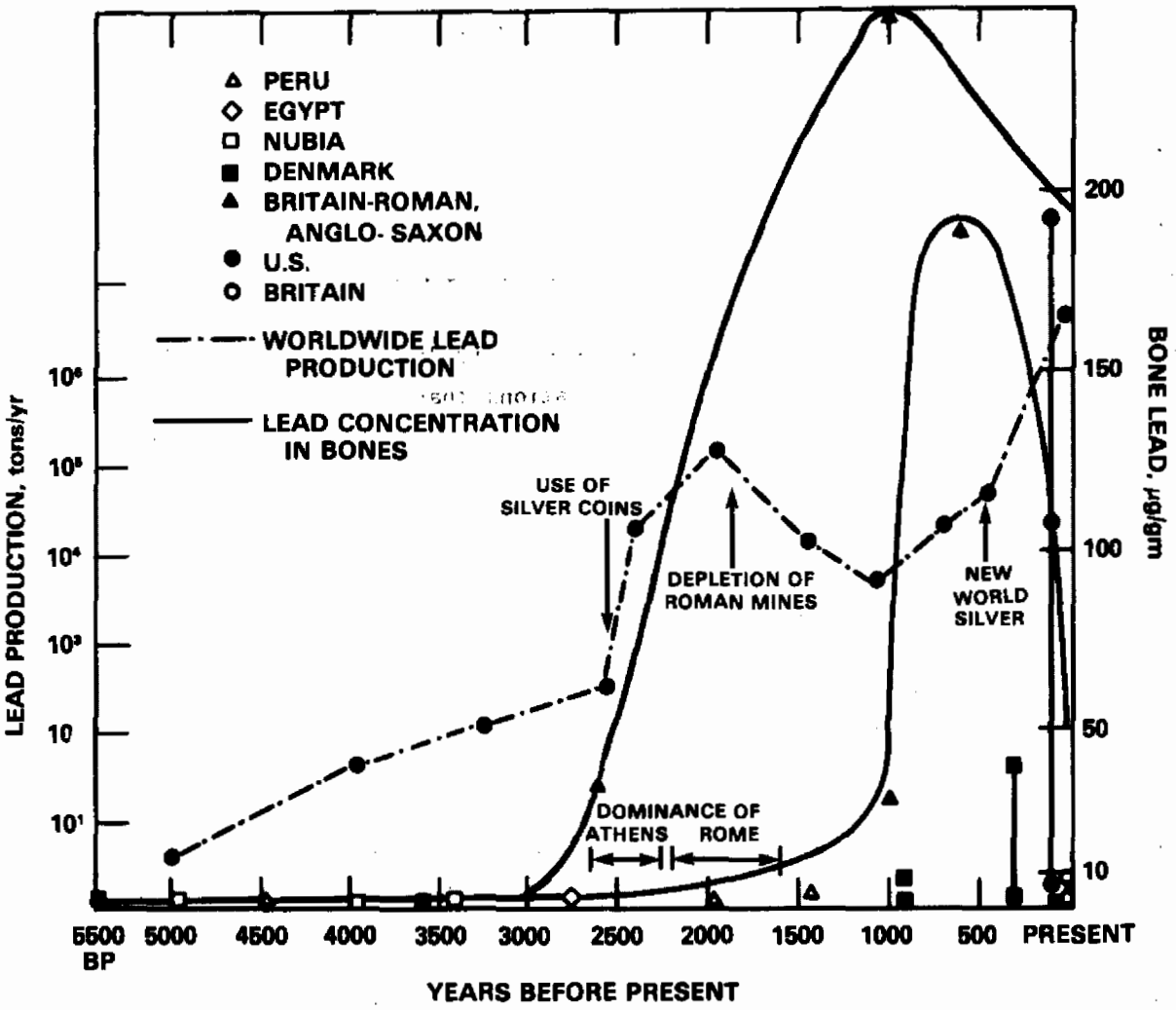

Figure 11-2. Estimate of world-wide lead production and lead concentrations in bones (μg/gm) from 5500 years before present to the present time.

Source: Adapted from Angle and McIntire (1982).

populations between 1 and 5 μg/dl, which is an order of magnitude below current U.S. urban population means. These studies are presented in detail in Section 11.3.2.2.

11.3.2.1 Ancient Populations. Table 11-1 presents summaries of several studies that analyzed bones and teeth to yield approximate estimates of lead absorption in the past. Some of these studies also analyzed contemporary current samples so that a comparison between past and present could be made.

Samples from the Sudan (ancient Nubians) were collected from several different periods (Grandjean et al., 1978). The oldest sample (3300-2900 B.C.) averaged 0.6 μg/g for bone and 0.9 μg/g for teeth. Data from the later time of 1650-1350 B.C. show a substantial increase in absorbed lead. Comparison of even the most recent ancient samples with a current Danish sample show a 4- to 8-fold increase over time.

Similar data were also obtained from Peruvian and Pennsylvania samples (Becker et al., 1968). The Peruvian and Pennsylvania samples were approximately from the same era (~1200-1400 A.D.). Little lead was used in these cultures as reflected by chemical analysis of bone lead content. The values were less than 5 μg/g for both samples. In contrast, modern samples from Syracuse, New York, ranged from 5 to 110 μg/g.

Fosse and Wesenberg (1981) reported a study of Norwegian samples from several eras. The oldest material was significantly lower in lead than modern samples. Ericson et al. (1979) also analyzed bone specimens from ancient Peruvians. Samples from 4500-3000 years ago to about 1400 years ago were reasonably constant (<0.2 μg/g).

Aufderheide et al. (1981) report a study of 16 skeletons from colonial America. Two social groups, identified as plantation proprietors and laborers, had distinctly different diet exposures to lead as shown by the analyses of the skeletal samples. The proprietor group averaged 185 μg/g bone ash while the laborer group averaged 35 μg/g.

Shapiro et al. (1975) report a study that contrasts teeth lead content of ancient populations with that of current remote populations and, also, with current urban populations. The ancient Egyptian samples (1st and 2nd millenia) exhibited the lowest teeth lead levels, mean of 9.7 μg/g. The more recent Peruvian Indian samples (12th Century) had similar levels (13.6 μg/g). The contemporary Alaskan Eskimo samples had a mean of 56.0 μg/g while Philadelphia samples had a mean of 188.3 μg/g. These data suggest an increasing pattern of lead absorption from ancient populations to current remote and urban populations.

11.3.2.2 Remote Populations. Several studies have looked at the blood lead levels in current remote populations (Piomelli et al., 1980; Poole and Smythe, 1980). These studies are important in defining the baseline level of internal lead exposures found in the world today.

TABLE 11-1. STUDIES OF PAST EXPOSURES TO LEAD

Population Studied	Age of Sample	Index of Exposure Used	Method of Analysis	Lead Levels	
				Pb µg/g dry wt.	
				Bone	Tooth
Nubians[1] vs. Modern Danes	3300 B.C. to 750 A.D. (5000 yrs. old)	Teeth (circum-pupil dentine)	FASS ASV		
Nubians					
A-group	3300 to 2900 B.C.	Bone (temporal)		0.6	0.9
C-group	2000 to 1600 B.C.			1.0	2.1
Pharonic	1650 to 1350 B.C.			2.0	5.0
Merotic, X-group & Christians	1 to 750 A.D.			1.2	3.2
Danes	Contemporary			5.5	25.7
				Bone µg/g	
Ancient Peruvians[2]	500-600 yrs. old	Bone (Tibia)	Arc emission spectroscopy	Peru	<5
Ancient Pennsylvanian Indians	500 yrs. old	(Femur)		Penn.	N.D.
Recent Syracuse,NY	Contemporary			Modern	110, 75, 5, 45, 16
					Tooth µg/g
Uvdal[3]	Buried from before 1200 A.D. to 1804	Teeth (Whole teeth, but values corrected for enamel and dentine)	AAS Arm		1.22
Modern Buskend County	Contemporary				4.12
Bryggen (medieval Bergen) Norway	?				1.81
	Contemporary				3.73

[1]Grandjean, P.; Nielsen, O.V.; Shapiro, I.M. (1978) Lead retention in ancient Nubian and contemporary populations. J. Environ. Pathol. Toxicol. 2: 781-787.

[2]Becker, R.O.; Spadaro, J.A.; Berg, E.W. (1968) The trace elements in human bone. J. Bone Jt. Surg. 50A: 326-334.

[3]Fosse, G.; Wesenberg, G.B.R. (1981) Lead, cadmium, zinc and copper in deciduous teeth of Norwegian children in the pre-industrial age. Int. J. Environ. Stud. 16: 163-170.

Piomelli et al. (1980) report a study of blood lead levels of natives in a remote (far from industrialized regions) section of Nepal. Portable air samplers were used to determine the air lead exposure in the region. The lead content of the air samples proved to be less than the detection limit, 0.004 $\mu g/m^3$. A later study by Davidson et al. (1981) from Nepal confirmed the low air lead levels reported by Piomelli et al. (1980). Davidson et al. (1981) found an average air lead concentration of 0.00086 $\mu g/m^3$.

Blood lead levels reported by Piomelli et al. (1980) for the Nepalese natives were low; the geometric mean blood lead for this population was 3.4 µg/dl. Adult males had a geometric mean of 3.8 µg/dl and adult females, 2.9 µg/dl. Children had a geometric mean blood lead of 3.5 µg/dl. Only 10 of 103 individuals tested had a blood lead level greater than 10 µg/dl. The blood samples, which were collected on filter paper discs, were analyzed by a modification of the Delves Cup Atomic Absorption Spectrophotometric method. Stringent quality control procedures were followed for both the blood and air samples.

To put these Nepalese values in perspective, Piomelli et al. (1980) reported analyses of blood samples collected and analyzed by the same methods from Manhattan, New York. New York blood leads averaged about 15 µg/dl, a 5-fold increase over the Nepalese values.

Poole and Smythe (1980) reported another study of a remote population, using contamination-free micro-blood sampling and chemical analysis techniques. They reported acceptable precision at blood lead concentrations as low as 5 µg/dl, using spectrophotometry. One hundred children were sampled from a remote area of Papua, New Guinea. Almost all of the children came from families engaging in subsistence agriculture. The children ranged from 7 to 10 years and included both sexes. Blood lead levels ranged from 1 to 13 µg/dl with a mean of 5.2. Although the data appear to be somewhat skewed to the right, they are in good agreement with those of Piomelli for Nepalase subjects.

11.3.3 Levels of Lead and Demographic Covariates in U.S. Populations

11.3.3.1 The NHANES II Study. The National Center for Health Statistics has provided the best currently available picture of blood lead levels among United States residents as part of the second National Health and Nutrition Examination Study (NHANES II) conducted from February 1976 to February 1980 (Mahaffey et al., 1982; McDowell et al., 1981; Annest et al., 1982). These are the first national estimates of lead levels in whole blood from a representative sample of the non-institutionalized U.S. civilian population aged 6 months to 74 years of age.

From a total of 27,801 persons identified through a stratified, multi-stage probability cluster sample of households throughout the U.S., blood lead determinations were scheduled for 16,563 persons including all children ages 6 months to 6 years, and one-half of all persons ages 7 to 74. Sampling was scheduled in 64 sampling areas over the 4-year period according to

a previously determined itinerary to maximize operational efficiency and response of participants. Because of the constraints of cold weather, the examination trailers traveled in the moderate climate areas during the winter, and the more northern areas during the summer (McDowell et al., 1981).

All reported blood lead levels were based on samples collected by venipuncture. Blood lead levels were determined by atomic absorption spectrophotometry using a modified Delves Cup micro-method. Specimens were analyzed in duplicate, with both determinations done independently in the same analytical run. Quality control was maintained by two systems, a bench system and a blind insertion of samples. If the NHANES II replicates differed by more than 7 µg/dl, the analysis was repeated for the specimen (about 0.3 percent were reanalyzed). If the average of the replicate values of either "bench" or "blind" control specimens fell outside previously established 95 percent confidence limits, the entire run was repeated. The estimated coefficient of variation for the "bench" quality control ranged from 7 to 15 percent (Mahaffey et al., 1979).

The reported blood lead levels were based on the average of the replicates. Blood lead levels and related data were reported as population estimates; findings for each person were inflated by the reciprocal of selection probabilities, adjusted to account for persons who were not examined and poststratified by race, sex and age. The final estimates closely approximate the U.S. Bureau of Census estimates for the civilian non-institutionalized population of the United States as of March 1, 1978, aged 1/2 to 74 years.

Participation rates varied across age categories; the highest non-response rate (51 percent) was for the youngest age group, 6 months through 5 years. Among medically examined persons, those with missing blood lead values were randomly distributed by race, sex, degree of urbanization and annual family income. These data are probably the best estimates now available regarding the degree of lead absorption in the general United States population.

Forthofer (1983) has studied the potential effects of non-response bias in the NHANES II survey and found no large biases in the health variables. This was based on the excellent agreement of the NHANES II examined data, which had a 27 percent non-response rate, with the National Health Interview Survey data, which had a 4 percent non-response rate.

The national estimates presented below are based on 9,933 persons whose blood lead levels ranged from 2.0 to 66.0 µg/dl. The median blood lead for the entire U.S. population is 13.0 µg/dl. It is readily apparent that blacks have a higher blood lead level than whites (medians for blacks and whites were 15.0 and 13.0 µg/dl, respectively).

Tables 11-2 through 11-4 display the observed distribution of measured blood lead levels by race, sex and age. The possible influence of measurement error on the percent distribution estimates is discussed in Section 11.3.5. Estimates of mean blood lead levels differ substantially with respect to age, race and sex. Blacks have higher levels than whites, the

TABLE 11-2. NHANES II BLOOD LEAD LEVELS OF PERSONS 6 MONTHS-74 YEARS, WITH WEIGHTED ARITHMETIC MEAN, STANDARD ERROR OF THE MEAN, WEIGHTED GEOMETRIC MEAN, MEDIAN, AND PERCENT DISTRIBUTION, BY RACE AND AGE, UNITED STATES, 1976-80

Race and age	Estimated population in thousands[a]	Number examined[b]	Blood lead level (μg/dl)								
			Arithmetic Mean	Standard error of the mean	Geometric Mean	Median	Less than 10	10-19	20-29	30-39	40+
							Percent distribution[d]				
All races[c]											
All ages	203,554	9,933	13.9	0.24	12.8	13.0	22.1	62.9	13.0	1.6	0.3
6 months-5 years	16,852	2,372	16.0	0.42	14.9	15.0	12.2	63.3	20.5	3.6	0.4
6-17 years	44,964	1,720	12.5	0.30	11.7	12.0	27.6	64.8	7.1	0.5	-
18-74 years	141,728	5,841	14.2	0.25	13.1	13.0	21.2	62.3	14.3	1.8	0.4
White											
All ages	174,528	8,369	13.7	0.24	12.6	13.0	23.3	62.8	12.2	1.5	0.3
6 months-5 years	13,641	1,876	14.9	0.43	14.0	14.0	14.5	67.5	16.1	1.8	0.2
6-17 years	37,530	1,424	12.1	0.30	11.3	11.0	30.4	63.4	5.8	0.4	-
18-74 years	123,357	5,069	14.1	0.25	12.9	13.0	21.9	62.3	13.7	1.8	0.4
Black											
All ages	23,853	1,332	15.7	0.48	14.6	15.0	13.3	63.7	20.0	2.3	0.6
6 months-5 years	2,584	419	20.9	0.61	19.6	20.0	2.5	45.4	39.9	10.2	2.0
6-17 years	6,529	263	14.8	0.53	14.0	14.0	12.8	70.9	15.6	0.7	-
18-74 years	14,740	650	15.5	0.54	14.4	14.0	14.7	62.9	19.6	2.0	0.9

[a] At the midpoint of the survey, March 1, 1978.

[b] With lead determinations from blood specimens drawn by venipuncture.

[c] Includes date for races not shown separately.

[d] Numbers may not add to 100 percent due to rounding.

TABLE 11-3. NHANES II BLOOD LEAD LEVELS OF MALES 6 MONTHS-74 YEARS, WITH WEIGHTED ARITHMETIC MEAN, STANDARD ERROR OF THE MEAN, WEIGHTED GEOMETRIC MEAN, MEDIAN, AND PERCENT DISTRIBUTION, BY RACE AND AGE, UNITED STATES, 1975-80

Race and age	Estimated population in thousands[a]	Number examined[b]	Blood lead level (μg/dl)								
			Arithmetic Mean	Standard error of the mean	Geometric Mean	Median	Less than 10	10-19	20-29	30-39	40+
							Percent distribution[d]				
All races[c]											
All ages	99,062	4,945	16.1	0.26	15.0	15.0	10.4	65.4	20.8	2.8	0.5
6 months-5 years	8,621	1,247	16.3	0.46	15.1	15.0	11.0	63.5	21.2	4.0	0.3
6-17 years	22,887	902	13.6	0.32	12.8	13.0	19.1	70.1	10.2	0.7	-
18-74 years	67,555	2,796	16.8	0.28	15.8	16.0	7.6	64.1	24.2	3.4	0.6
White											
All ages	85,112	4,153	15.8	0.27	14.7	15.0	11.3	66.0	19.6	2.6	0.4
6 months-5 years	6,910	969	15.2	0.46	14.2	14.0	13.0	67.6	17.3	2.0	0.1
6-17 years	19,060	753	13.1	0.33	12.4	13.0	21.4	69.5	8.4	0.7	-
18-74 years	59,142	2,431	16.6	0.29	15.6	16.0	8.1	64.8	23.3	3.3	0.6
Black											
All ages	11,171	664	18.3	0.52	17.3	17.0	4.0	59.6	31.0	4.1	1.3
6 months-5 years	1,307	231	20.7	0.74	19.3	19.0	2.7	48.8	35.1	11.1	2.4
6-17 years	3,272	129	16.0	0.62	15.3	15.0	8.0	69.9	21.1	1.0	-
18-74 years	6,592	304	19.1	0.70	18.1	18.0	2.3	56.4	34.9	4.5	1.8

[a] At the midpoint of the survey, March 1, 1978.

[b] With lead determinations from blood specimens drawn by venipuncture.

[c] Includes date for races not shown separately.

[d] Numbers may not add to 100 percent due to rounding.

TABLE 11-4. NHANES II BLOOD LEAD LEVELS OF FEMALES 6 MONTHS-74 YEARS, WITH WEIGHTED ARITHEMETIC MEAN, STANDARD ERROR OF THE MEAN, WEIGHTED GEOMETRIC MEAN, MEDIAN, AND PERCENT DISTRIBUTION, BY RACE AND AGE, UNITED STATES, 1976-80

Race and age	Estimated population in thousands[a]	Number examined[b]	Blood lead level (µg/dl)								
			Arithmetic Mean	Standard error of the mean	Geometric Mean	Median	Less than 10	10-19	20-29	30-39	40+
All races[c]							Percent distribution[d]				
All ages	104,492	4,988	11.9	0.23	11.1	11.0	33.3	60.5	5.7	0.4	0.2
6 months-5 years	8,241	1,125	15.8	0.42	14.6	15.0	13.5	63.2	19.8	3.0	0.5
6-17 years	22,077	818	11.4	0.32	10.6	11.0	36.6	59.3	3.9	0.2	-
18-74 years	74,173	3,045	11.8	0.22	11.0	11.0	33.7	60.6	5.2	0.3	0.2
White											
All ages	89,417	4,216	11.7	0.23	10.9	11.0	34.8	59.6	5.0	0.4	0.2
6 months-5 years	6,732	907	14.7	0.44	13.7	14.0	16.1	67.3	14.8	1.6	0.2
6-17 years	18,470	671	11.0	0.31	10.3	11.0	40.0	56.9	2.9	0.2	-
18-74 years	64,215	2,638	11.7	0.23	10.9	11.0	34.6	59.9	5.0	0.4	0.2
Black											
All ages	12,682	668	13.4	0.45	12.6	13.0	21.5	67.3	10.3	0.7	0.1
6 months-5 years	1,277	188	21.0	0.69	19.8	20.0	2.2	41.6	45.3	9.2	1.7
6-17 years	3,256	134	13.6	0.64	12.8	13.0	17.7	71.9	10.0	0.4	-
18-74 years	8,148	346	12.7	0.44	12.0	12.0	24.7	68.1	7.2	-	-

[a] At the midpoint of the survey, March 1, 1978.

[b] With lead determinations from blood specimens drawn by venipuncture.

[c] Includes date for races not shown separately.

[d] Numbers may not add to 100 percent due to rounding.

6-month to 5-year group is higher than the older age groups, and men are higher than women. Overall, younger children show only a slight age effect, with 2- to 3-year-olds having slightly higher blood lead levels than older children or adults (see Figure 11-3). In the 6-17 year grouping there is a decreasing trend in lead levels with increasing age. Holding age constant, there are significant race and sex differences; as age increases, the difference in mean blood leads between males and females increases.

For adults 18-74 years, males have greater blood lead levels than females for both whites and blacks. There is a significant relationship between age and blood lead, but it differs for whites and blacks. Whites display increasing blood lead levels until 35-44 years of age and then a decline, while blacks have increasing blood lead levels until 55-64.

This study showed a clear relationship between blood lead level and family income group. For both blacks and whites, increasing family income is associated with lower blood lead level. At the highest income level the difference between blacks and whites is the smallest, although blacks still have significantly higher blood lead levels than whites. The racial difference was greatest for the 6-month to 5-year age range.

The NHANES II blood lead data were also examined with respect to the degree of urbanization at the place of residence. The three categories used were urban areas with population greater than one million, urban areas with population less than one million and rural areas. Geometric mean blood lead levels increased with degree of urbanization for all race-age groups except for blacks 18-74 years of age (see Table 11-5). Most importantly, urban black children aged 6 months to 5 years appeared to have distinctly higher mean blood lead levels than any other population subgroup.

11.3.3.2 The Childhood Blood Lead Screening Programs. In addition to the nationwide picture presented by the NHANES II (Annest et al., 1982) study regarding important demographic correlates of blood lead levels, Billick et al. (1979, 1982) provide large scale analyses of blood lead values in specific cities that also address this issue.

Billick et al. (1979) analyzed data from New York City blood lead screening programs from 1970 through 1976. The data include age in months, sex, race, residence expressed as health district, screening information and blood lead values expressed in intervals of 10 mg/dl. Only the venous blood lead data (178,588 values), clearly identified as coming from the first screening of a given child, were used. All blood lead determinations were done by the same laboratory. Table 11-6 presents the geometric means of the children's blood lead levels by age, race and year of collection. The annual means were calculated from the four quarterly means which were estimated by the method of Hasselblad et al. (1980).

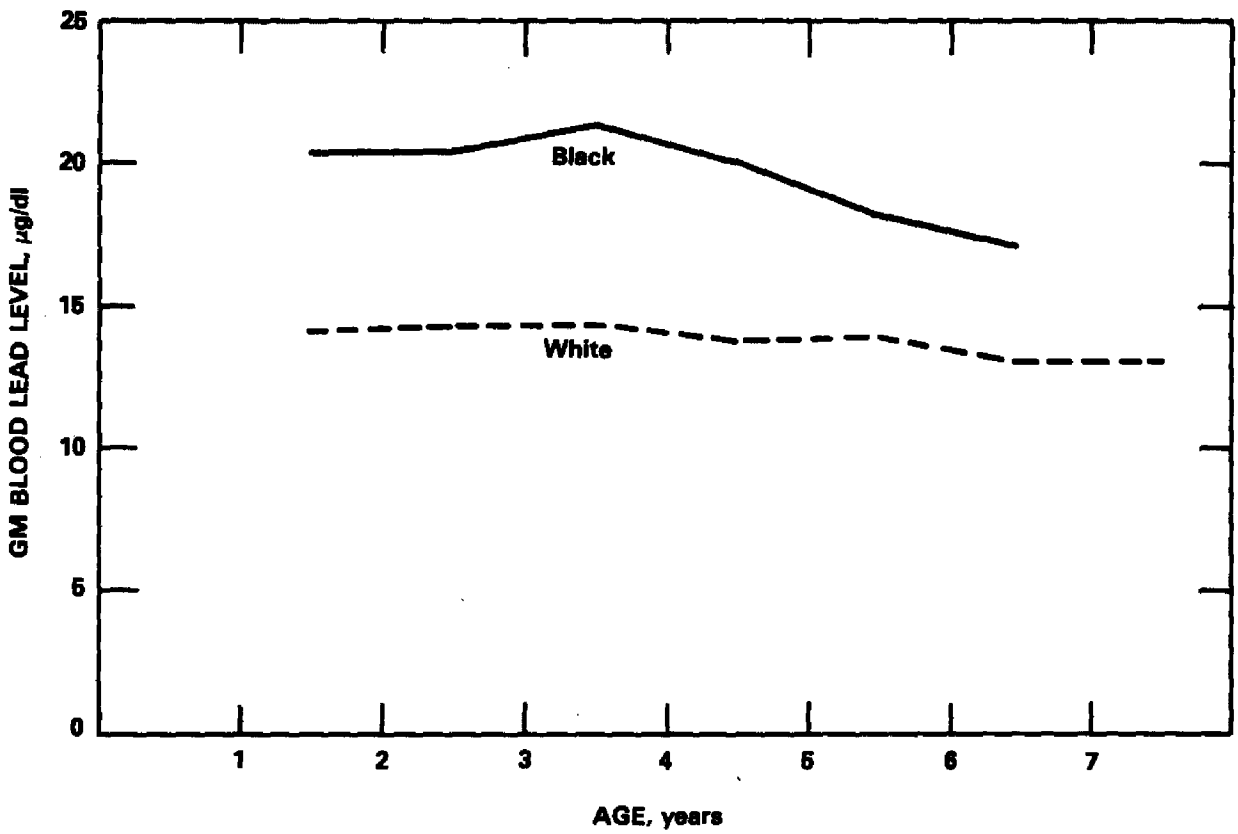

Figure 11-3. Geometric mean blood lead levels by race and age for younger children in the NHANES II study. The data were furnished by the National Center of Health Statistics.

TABLE 11-5. WEIGHTED GEOMETRIC MEAN BLOOD LEAD LEVELS FROM NHANES II SURVEY BY DEGREE OF URBANIZATION OF PLACE OF RESIDENCE IN THE U.S. BY AGE AND RACE, UNITED STATES 1976-80

Race and age	Degree of urbanization					
	Urban, ≥1 million		Urban, <1 million		Rural	
All races	Geometric mean (µg/dl)					
All ages	14.0	(2,395)[a]	12.8	(3,869)	11.9	(3,669)
6 months-5 years	16.8	(544)	15.3	(944)	13.1	(884)
6-17 years	13.1	(414)	11.7	(638)	10.7	(668)
18-74 years	14.1	(1,437)	12.9	(2,287)	12.2	(2,117)
Whites						
All ages	14.0	(1,767)	12.5	(3,144)	11.7	(3,458)
6 months-5 years	15.6	(358)	14.4	(699)	12.7	(819)
6-17 years	12.7	(294)	11.4	(510)	10.5	(620)
18-74 years	14.3	(1,115)	12.7	(1,935)	12.1	(2,019)
Blacks						
All ages	14.4	(570)	14.7	(612)	14.4	(150)
6 months-5 years	20.9	(172)	19.3	(205)	16.4	(42)
6-17 years	14.6	(111)	13.6	(113)	12.9	(39)
18-74 years	13.9	(287)	14.7	(294)	14.9	(69)

[a]Number with lead determinations from blood specimens drawn by venipuncture.

Source: Annest et al., 1982.

TABLE 11-6. ANNUAL GEOMETRIC MEAN BLOOD LEAD LEVELS FROM THE NEW YORK BLOOD LEAD SCREENING STUDIES OF BILLICK ET AL. (1979). ANNUAL GEOMETRIC MEANS ARE CALCULATED FROM QUARTERLY GEOMETRIC MEANS ESTIMATED BY THE METHOD OF HASSELBLAD ET AL. (1980)

Ethnic group	Year	Geometric mean blood lead level, µg/100 ml							
		1-12 mo	13-24 mo	25-36 mo	37-48 mo	49-60 mo	61-72 mo	73- mo	All ages
Black	1970	25.2	28.9	30.1	28.3	27.8	26.4	25.9	27.5
	1971	24.0	29.3	29.9	29.3	28.2	27.2	26.5	27.7
	1972	22.2	26.0	26.3	25.4	24.7	23.9	23.3	24.5
	1973	22.9	26.6	26.0	25.3	24.4	24.1	23.3	24.6
	1974	22.0	25.5	25.4	24.3	23.4	21.8	21.9	23.4
	1975	19.8	22.4	22.4	21.9	21.2	21.4	18.9	21.1
	1976	16.9	20.0	20.6	20.2	19.5	18.2	18.4	19.1
Hispanic	1970	20.8	23.8	24.5	24.7	23.8	23.6	23.0	23.4
	1971	19.9	22.6	24.6	24.4	23.9	23.4	23.5	23.1
	1972	18.7	20.5	21.8	22.2	21.8	21.8	21.0	21.1
	1973	20.2	21.8	22.5	22.8	22.0	21.5	21.7	21.8
	1974	19.8	21.5	22.7	22.5	21.9	20.5	20.2	21.3
	1975	16.3	18.7	19.9	20.1	19.8	19.2	17.2	18.7
	1976	16.0	17.4	18.1	18.2	18.0	16.7	17.2	17.4
White	1970	21.1	25.2	26.0	24.8	26.0	22.6	21.3	23.8
	1971	22.5	22.7	22.7	23.5	21.6	21.3	19.5	21.9
	1972	20.1	21.6	20.7	20.8	21.0	20.2	17.3	20.2
	1973	21.5	21.8	21.7	20.2	21.3	20.7	18.4	20.8
	1974	20.4	21.7	21.3	21.1	20.6	19.5	17.3	20.2
	1975	19.3	17.9	16.1	18.5	16.8	15.4	15.9	17.1
	1976	15.2	18.2	17.1	16.6	16.2	15.9	8.8	15.1

All racial/ethnic groups show an increase in geometric mean blood level with age for the first two years and a general decrease in the older age groups. Figure 11-4 shows the trends for all years (1970-1976) combined.

The childhood screening data described by Billick et al. (1979) show higher geometric mean blood lead values for blacks than for Hispanics or for whites. Table 11-6 also presents these geometric means for the three racial/ethnic groups for seven years. Using the method of Hasselblad et al. (1980), the estimated geometric standard deviations were 1.41, 1.42 and 1.42 for blacks, Hispanics and whites, respectively.

11.3.4 Time Trends

In the past few years a number of reports have appeared that examined trends in blood lead levels during the 1970's. In several of these reports some environmental exposure estimates are available.

11.3.4.1 Time Trends in the Childhood Lead Poisoning Screening Programs. Billick and colleagues have analyzed the results of blood lead screening programs conducted by the City of New York (Billick et al., 1979; Billick 1982). Most details regarding this data set were already described, but Table 11-7 summarizes relevant methodologic information for these analyses and for analyses done on a similar data base from Chicago, Illinois. The discussion of the New York data below is limited to an exposition of the time trend in blood lead levels from 1970 to 1977.

Geometric mean blood lead levels decreased for all three racial groups and for almost all age groups in the period 1970-76 (Table 11-6). Table 11-8 shows that the downward trend covers the entire range of the frequency distribution of blood lead levels. The decline in blood lead levels showed seasonal variability, but the decrease in time was consistent for each season. The 1977 data were supplied to EPA by Dr. Billick.

In addition to this time trend observed in New York City, Billick (1982) examined similar data from Chicago and Louisville. The Chicago data set was much more complete than the Louisville one, and was much more methodologically consistent. Therefore, only the Chicago data will be discussed here. The lead poisoning screening program in Chicago may be the longest continuous program in the United States. Data used in this report covered the years 1967-1980. Because the data set was so large, only a 1 in 30 sample of laboratory records was coded for statistical analysis (similar to procedures used for New York described above).

The blood lead data for Chicago contains samples that may be repeats, confirmatory analyses, or even samples collected during treatment, as well as initial screening samples. This is a major difference from the New York City data, which had initial screening values only.

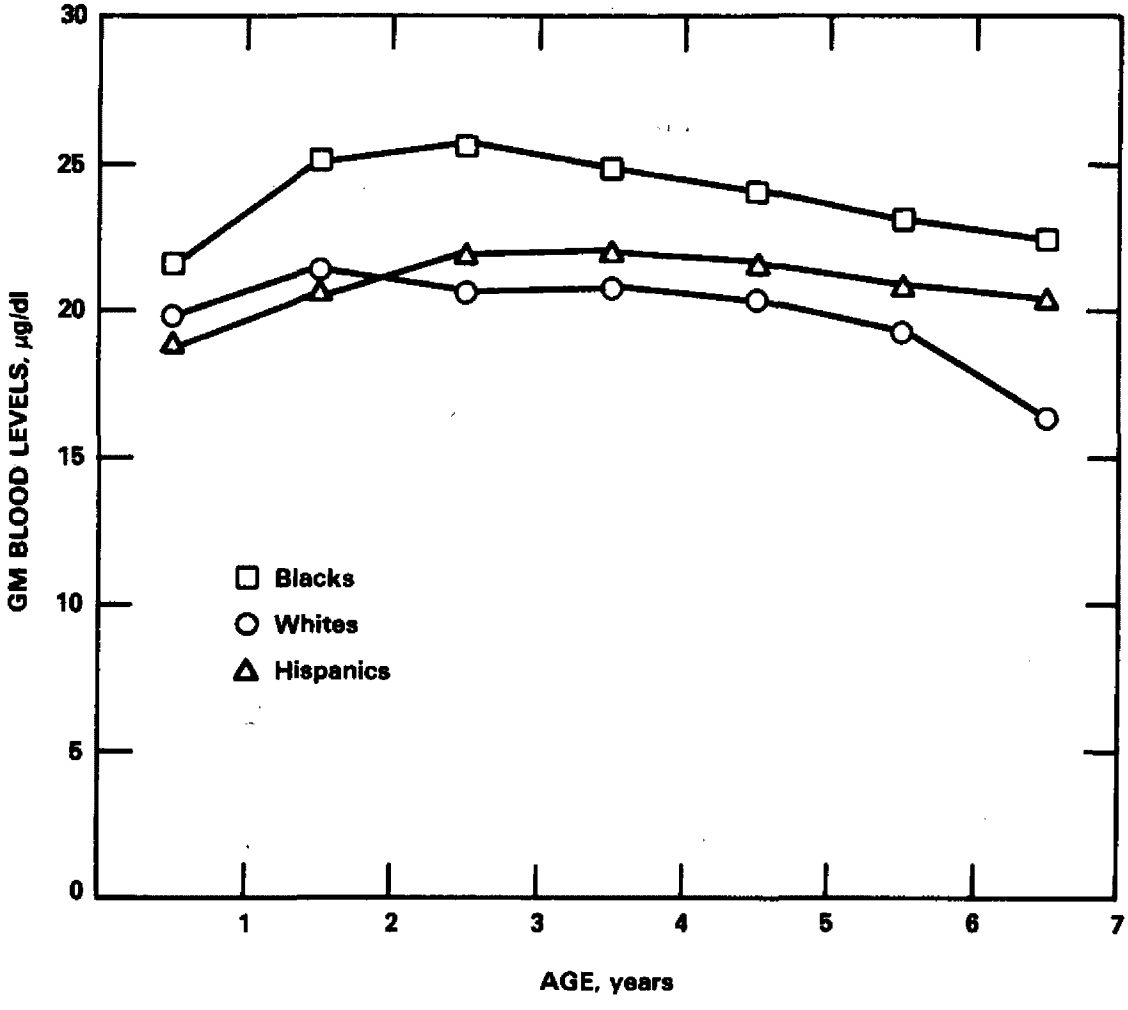

Figure 11-4. Geometric mean blood lead values by race and age for younger children in the New York City screening program (1970-1976).

TABLE 11-7. CHARACTERISTICS OF CHILDHOOD LEAD POISONING SCREENING DATA

	New York	Chicago
Time period	1970 - 1979	1967 - 1980 (QTR 2)
Sampling technique	Venous	Venous
Analytic technique	AAS (Hasel method)	AAS (Hasel method)
Laboratory	In house	In house
Screening status	Available/unknown	Unavailable
Race classification and total number of samples used in analysis*	Unknown 69,658 White 5,922 Black 51,210 Hispanic 41,364 Other 4,398 TOTAL 172,552	Nonblack 6,459 Black 20,353 TOTAL 26,812
Raw data	Decade grouped	Ungrouped
Gasoline data	Tri-state (NY, NJ, CT) 1970 - 1979 SMSA 1974 - 1979	SMSA

*New York data set only includes first screens while Chicago includes also confirmatory and repeat samples.

TABLE 11-8. DISTRIBUTION OF BLOOD LEAD LEVELS FOR 13 TO 48 MONTH OLD BLACKS BY SEASON AND YEAR* FOR NEW YORK SCREENING DATA

	January - March Percent			July - September Percent		
Year	<15µg/dl	15 to 34µg/dl	>34µg/dl	<15µg/dl	15 to 34µg/dl	>34µg/dl
1970	(insufficient sample size)			3.4	54.7	42.0
1971	3.8	69.5	26.7	1.3	56.0	42.7
1972	4.4	76.1	19.5	4.3	72.2	23.4
1973	7.3	80.3	12.4	2.7	62.4	34.9
1974	9.2	73.8	17.0	8.2	65.4	26.4
1975	11.1**	77.5**	11.4**	7.3**	81.3**	11.4**
1976	21.1	74.1	4.8	11.9	75.8	12.3
1977	28.4	66.8	4.8	19.9	72.9	7.2

* data provided by I.H. Billick

**Percents estimated using interpolation assuming a lognormal distribution.

Chicago blood lead levels were all obtained on venous samples and were analyzed by one laboratory, the Division of Laboratories, Chicago Department of Health. Lead determinations were done by atomic absorption. Racial composition was described in more detail than for New York, but analysis showed there was no difference among the non-blacks, so they were pooled in the final analysis.

Table 11-7 displays important characteristics of the Chicago and New York screening programs, including the number of observations involved in these studies. From tables in the appendices of the report (Billick, 1982), specific data on geometric mean blood lead values, race, sex and sampling data for both cities are available. Consistency of the data across cities is depicted in Figure 11-5. The long-term trends are quite consistent, although the seasonal peaks are somewhat less apparent.

11.3.4.2 Newark. Gause et al. (1977) present data from Newark, New Jersey, that reinforce the findings of Billick and coworkers. Gause et al. studied the levels of blood lead among 5- and 6-year-old children tested by the Newark Board of Education during the academic years 1973-74, 1974-75 and 1975-76. All Newark schools participated in all years. Participation rates were 34, 33 and 37 percent of the eligible children for the three years, respectively.

Blood samples were collected by fingerstick onto filter paper. The samples were then analyzed for lead by atomic absorption spectrophotometry. The authors point out that fingerstick samples are more subject to contamination than venous samples; and that because erythrocyte protoporphyrin confirmation of blood lead values greater than 50 µg/dl was not done until 1974, data from earlier years may contain somewhat higher proportions of false positives than later years.

Blood lead levels declined markedly during this 3-year period. In the three years covered by the study the percentage of children with blood lead levels less than 30 µg/dl went from 42 percent for blacks in 1973-74 to 71 percent in 1975-76; similarly, the percentages went from 56 percent to 85 percent in whites. The percentage of high risk children (>49 µg/dl) dropped from 9 to 1 percent in blacks and from 6 to 1 percent in whites during the study period.

Unfortunately, no companion analysis was presented regarding concurrent trends in environmental exposures. However, Foster et al. (1979) reported a study from Newark that examined the effectiveness of the city's housing deleading program, using the current blood lead status of children who had earlier been identified as having confirmed elevated blood lead levels; according to the deleading program, these children's homes should have been treated to alleviate the lead problem. After intensive examination, the investigators found that 31 of the 100 children studied had lead-related symptoms at the time of Foster's study. Examination of the records of the program regarding the deleading activity indicated a serious lack of compliance with the program requirements. Given the results of Foster's study, it seems unlikely that the observed trend was caused by the deleading program.

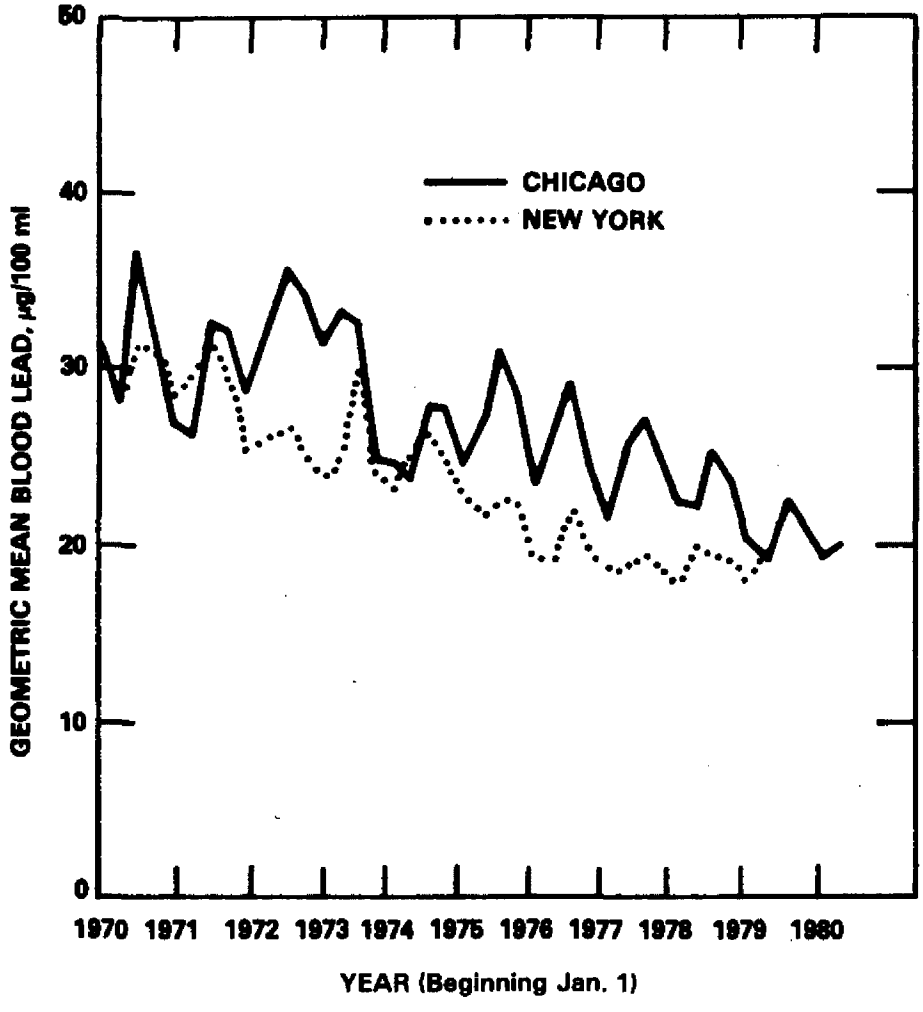

Figure 11-5. Time dependence of blood lead for blacks, aged 24 to 35 months, in New York City and Chicago.

Source: Adapted from Billick (1982).

11.3.4.3 Boston. Rabinowitz and Needleman (1982) report a study of umbilical cord blood lead levels from 11,837 births between April 1979 and April 1981 in the Boston area. These represent 97 percent of the births occurring in a hospital serving a diverse population. Blood samples were analyzed for lead by anodic stripping voltammetry after stringent quality control procedures were used. External quality control checks were done by participation in the Blood Lead Reference Program, conducted by the Centers for Disease Control. The average difference between the investigators' results and the reference lab was 1.4 μg/dl.

The overall mean blood lead concentration was 6.56 ± 3.19 (standard deviation) with a range from 0.0 to 37.0 μg/dl. A downward trend in umbilical cord blood lead levels (-0.89 μg/dl/yr) was noted over the two years of the study (see Figure 11-6).

11.3.4.4 NHANES II. Blood lead data from NHANES II (see Section 11.3.3.1) also show a significant downward trend over time (Annest et al., 1983). Predicted mean blood lead levels dropped from 14.6 μg/dl in February 1976 to 9.2 μg/dl in February of 1980. Mean values from these national data presented in 28 day intervals from February 1976 to February 1980 are displayed in Figure 11-7.

The decreases in average blood lead levels were found for both blacks and whites, all age groups and both sexes. Further statistical analysis suggested that the decline was not entirely due to season, income, geographic region or urban-rural differences. The analyses of the quality control data showed no trend in the blind quality control data.

A review panel has examined this data, and a report of their findings is in Appendix 11-D. The panel concluded that there was strong evidence of a downward trend during the period of the study. The panel further stated that the magnitude of this drop could be estimated, and that it appeared not only in the entire population, but in some major subgroups as well.

11.3.4.5 Other Studies. Oxley (1982) reported an English study that looks at the recent past time trend in blood lead levels. Preemployment physicals conducted in 1967-69 and 1978-80 provided the subjects for the study. Blood samples were collected by venipuncture. Different analytical procedures were used in the two surveys, but a comparison study showed that the data from one procedure could be reliably adjusted to the other procedure. The geometric mean blood lead levels declined from 20.2 to 16.6 μg/dl.

11.3.5 Distributional Aspects of Population Blood Lead Levels

The importance of the distribution form of blood lead levels was briefly discussed in Section 11.2.3. The distribution form determines which measure of central tendency (arithmetic mean, geometric mean, median) is most appropriate. It is even more important in estimating percentiles in the upper tail of the distribution, an issue of much importance in estimating percentages (or absolute numbers) of individuals in specific population groups likely to be experiencing various lead exposure levels.

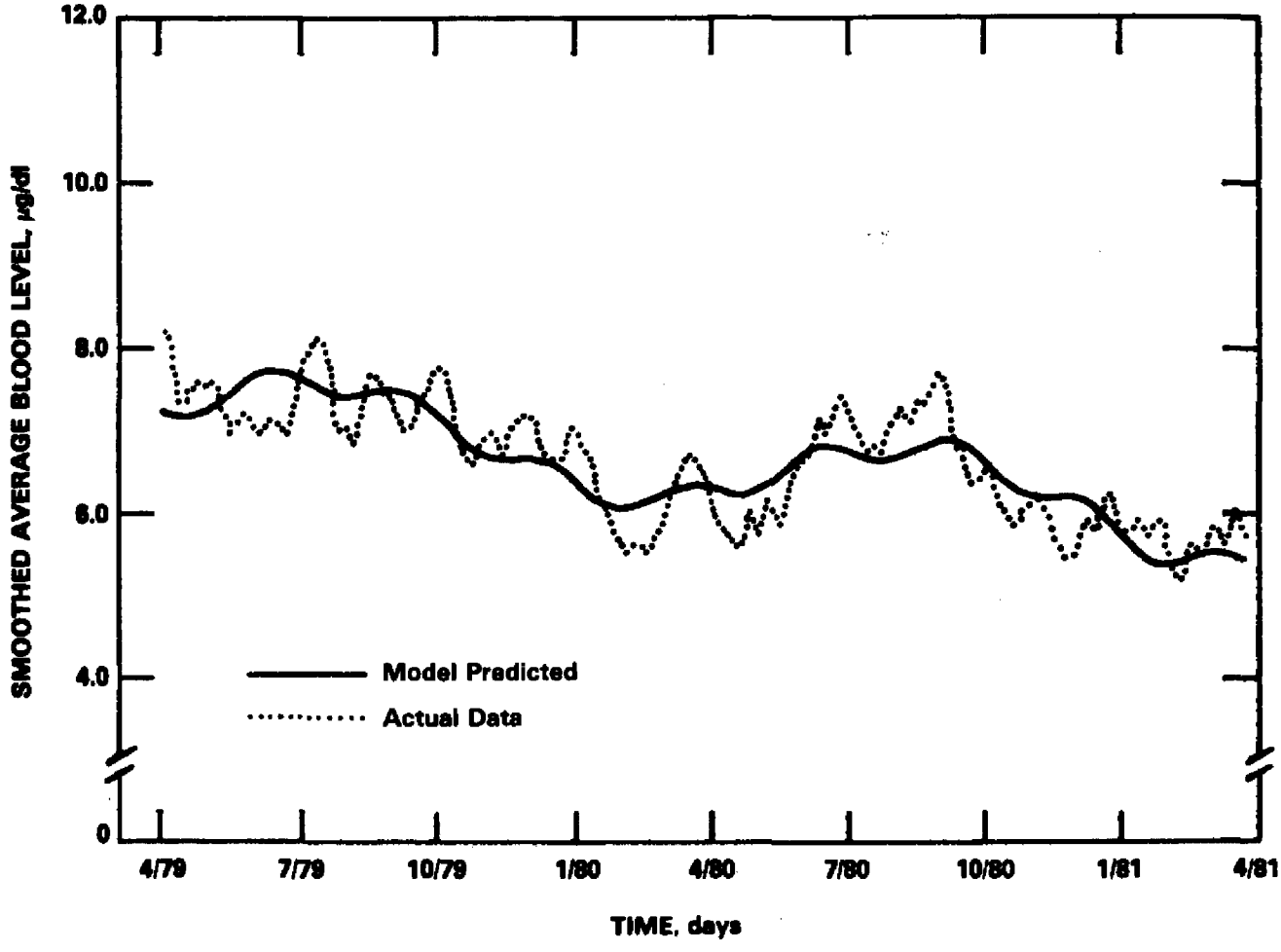

Figure 11-6. Modeled umbilical cord blood lead levels by date of sample collection for infants in Boston.

Source: Rabinowitz and Needleman (1982).

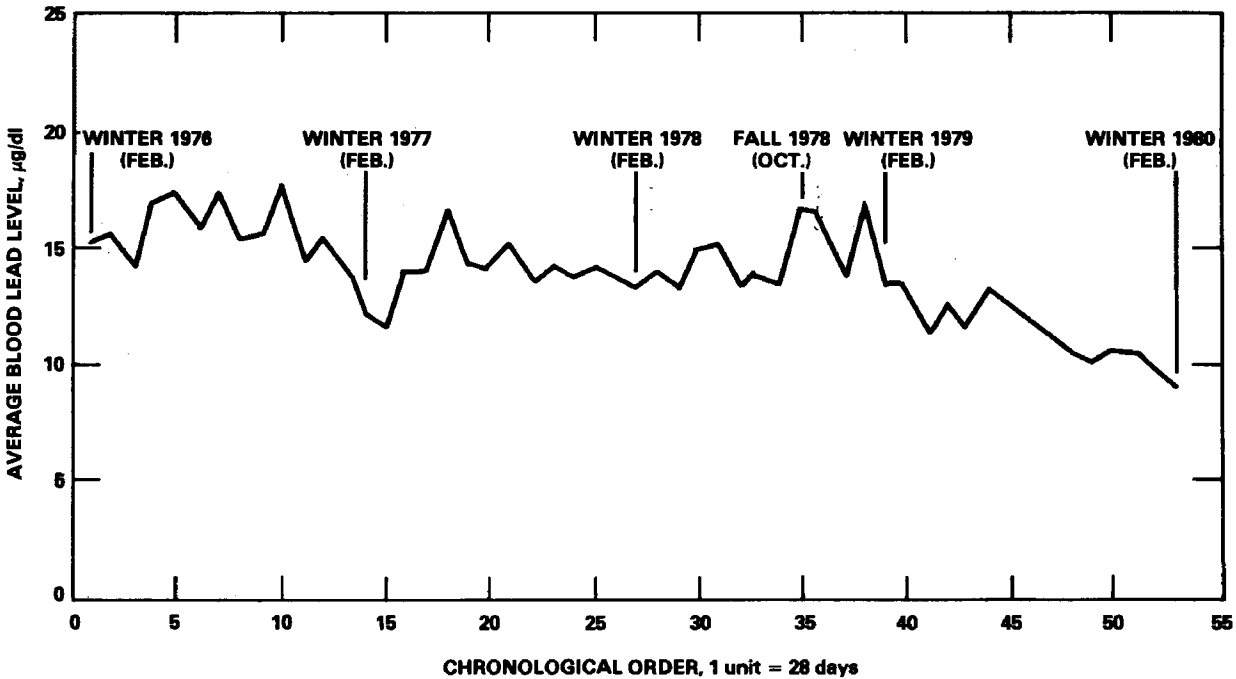

Figure 11-7. Average blood lead levels of U.S. population 6 months—74 years, United States, February 1976—February 1980, based on dates of examination of NHANES II examinees with blood lead determinations.

Source: Annest et al. (1983).

Distribution fitting requires large numbers of samples taken from a relatively homogeneous population. A homogeneous population is one in which the distribution of values remains constant when split into subpopulations. These subpopulations could be defined by demographic factors such as race, age, sex, income, degree of urbanization, and by degree of exposure. Since these factors always have some effect, a relatively homogeneous population will be defined as one with minimal effects from any factors that contribute to differences in blood lead levels.

Several authors have suggested that the distribution of blood lead levels for any relatively homogeneous population closely follows a lognormal distribution (Yankel et al., 1977; Tepper and Levin, 1975; Azar et al., 1975). Lognormality has been noted for other metals, such as ^{90}Sr, ^{144}Ce, Pu and Ti in various tissues of human populations (Cuddihy et al., 1979; Schubert et al., 1967). Yankel et al. (1977), Tepper and Levin (1975) and Angle and McIntire (1979) all found their blood lead data to be lognormally distributed. Further analysis by EPA of the Houston study of Johnson et al. (1974), the study of Azar et al. (1975) and the New York children screening program reported by Billick et al. (1979) also demonstrated that a lognormal distribution provided a good fit to the data.

The only nationwide survey of blood lead levels in the U.S. population is the NHANES II survey (Annest et al., 1982). In order to obtain a relatively homogeneous subpopulation of lower environmental exposure, the analysis was restricted to whites not living in an SMSA with a family income greater than $6,000 per year, the poverty threshold for a family of four at the midpoint of study as determined by the U.S. Bureau of Census. This subpopulation was split into four subgroups based on age and sex. The summary statistics for these subgroups are in Table 11-9.

Each of these four subpopulations were fitted to five different distributions: normal, lognormal, gamma, Weibull and Wald (Inverse Gaussian) as shown in Table 11-10. Standard chi-square goodness-of-fit tests were computed after collapsing the tails to obtain an expected cell size of five. The goodness-of-fit test and likelihood functions indicate that the lognormal distribution provides a better fit than the normal, gamma or Weibull. A histogram and the lognormal fit for each of the four subpopulations appear in Figure 11-8. The Wald distribution is quite similar to the lognormal distribution and appears to provide almost as good a fit. Table 11-10 also indicates that the lognormal distribution estimates the 99th percentile as well as any other distribution.

Based on the examination of the NHANES II data, as well as the results of several other papers, it appears that the lognormal distribution is the most appropriate for describing the distribution blood lead levels in homogeneous populations with relatively constant exposure levels.

The lognormal distribution appears to fit well across the entire range of the distribution, including the right tail. It should be noted, however, that the data being fitted are the result of both measurement variation and population variation. The measurement variation alone does not follow a lognormal distribution, as was shown by Saltzman et al., 1983.

TABLE 11-9. SUMMARY OF UNWEIGHTED BLOOD LEAD LEVELS IN WHITES NOT LIVING IN AN SMSA WITH FAMILY INCOME GREATER THAN $6,000

Subgroup	Sample Size	Unweighted Mean Arith. Mean µg/dl	Unweighted Mean Geom. Mean µg/dl	Sample Median µg/dl	99th %tile µg/dl	Arith. Std. Dev. µg/dl	Geom. Std. Dev. µg/dl
age 1/2 to 6	752	13.7	12.9	13.0	32.0	5.03	1.43
age 6 to 18	573	11.3	10.6	10.0	24.0	4.34	1.46
age 18+,men	922	15.7	14.7	15.0	35.8	5.95	1.44
age 18+,women	927	10.7	10.0	10.0	23.0	4.14	1.46

It is obvious that even relatively homogeneous populations have considerable variation among individuals. The estimation of this variation is important for determination of the upper tail of the blood lead distribution, the group at highest risk. The NHANES II study provides sufficent data to estimate this variation. In order to minimize the effects of location, income, sex and age, an analysis of variance procedure was used to estimate the variation for several age-race groups. The variables just mentioned were used as main effects, and the resulting mean square errors of the logarithms are in Table 11-11. The estimated geometric standard deviations represent the estimated variances for subgroups with comparable sex, age, income and place of residence. These are not necessarily representative of the variances seen for specific subgroups described in the NHANES II study.

Analytical variation, which exists in any measurement of any kind, has an impact on the bias and precision of statistical estimates. For this reason, it is important to estimate the magnitude of variation. Analytical variation consists of both measurement variation (variation between measurements run at the same time) and variation created by analyzing samples at different times (days). This kind of variation for blood lead determinations has been discussed by Lucas (1981).

The NHANES II survey is an example of a study with excellent quality control data. The analytical variation was estimated specifically for this study by Annest et al. (1983). The analytical variation was estimated as the sum of components estimated from the high and low

TABLE 11-10. SUMMARY OF FITS TO NHANES II BLOOD LEAD LEVELS OF WHITES NOT LIVING IN AN SMSA, INCOME GREATER THAN $6,000, FOR FIVE DIFFERENT TWO-PARAMETER DISTRIBUTIONS

Children <6 years

	Chi-square	D.F.	p-value	log-likelihood	deviation* at 99 %tile
Normal	75.52	8	0.0000	-2280.32	6.61
Lognormal	14.75	10	0.1416	-2210.50	2.57
Gamma	17.51	9	0.0413	-2216.51	4.68
Weibull	66.77	8	0.0000	-2271.57	5.51
Wald	15.71	10	0.1083	-2211.83	2.76

Children 6≤ years ≤17

	Chi-square	D.F.	p-value	log-likelihood	deviation* at 99 %tile
Normal	39.58	6	0.0000	-1653.92	2.58
Lognormal	3.22	8	0.9197	-1607.70	-1.50
Gamma	4.88	7	0.6745	-1609.33	-0.64
Weibull	24.48	6	0.0004	-1641.35	1.72
Wald	2.77	8	0.9480	-1609.64	-1.30

Men ≥18 years

	Chi-square	D.F.	p-value	log-likelihood	deviation* at 99 %tile
Normal	156.98	10	0.0000	-2952.85	6.24
Lognormal	12.22	13	0.5098	-2854.04	1.51
Gamma	34.26	12	0.0006	-2864.79	4.00
Weibull	132.91	11	0.0000	-2934.14	4.88
Wald	14.42	13	0.3450	-2855.94	1.72

Men ≥18 years

	Chi-square	D.F.	p-value	log-likelihood	deviation* at 99 %tile
Normal	66.31	5	0.0000	-2631.67	2.68
Lognormal	7.70	8	0.4632	-2552.12	-1.18
Gamma	11.28	7	0.1267	-2553.34	0.90
Weibull	56.70	6	0.0000	-2611.78	1.73
Wald	10.26	8	0.2469	-2556.88	-1.01

*observed 99th sample percentile minus predicted 99th percentile

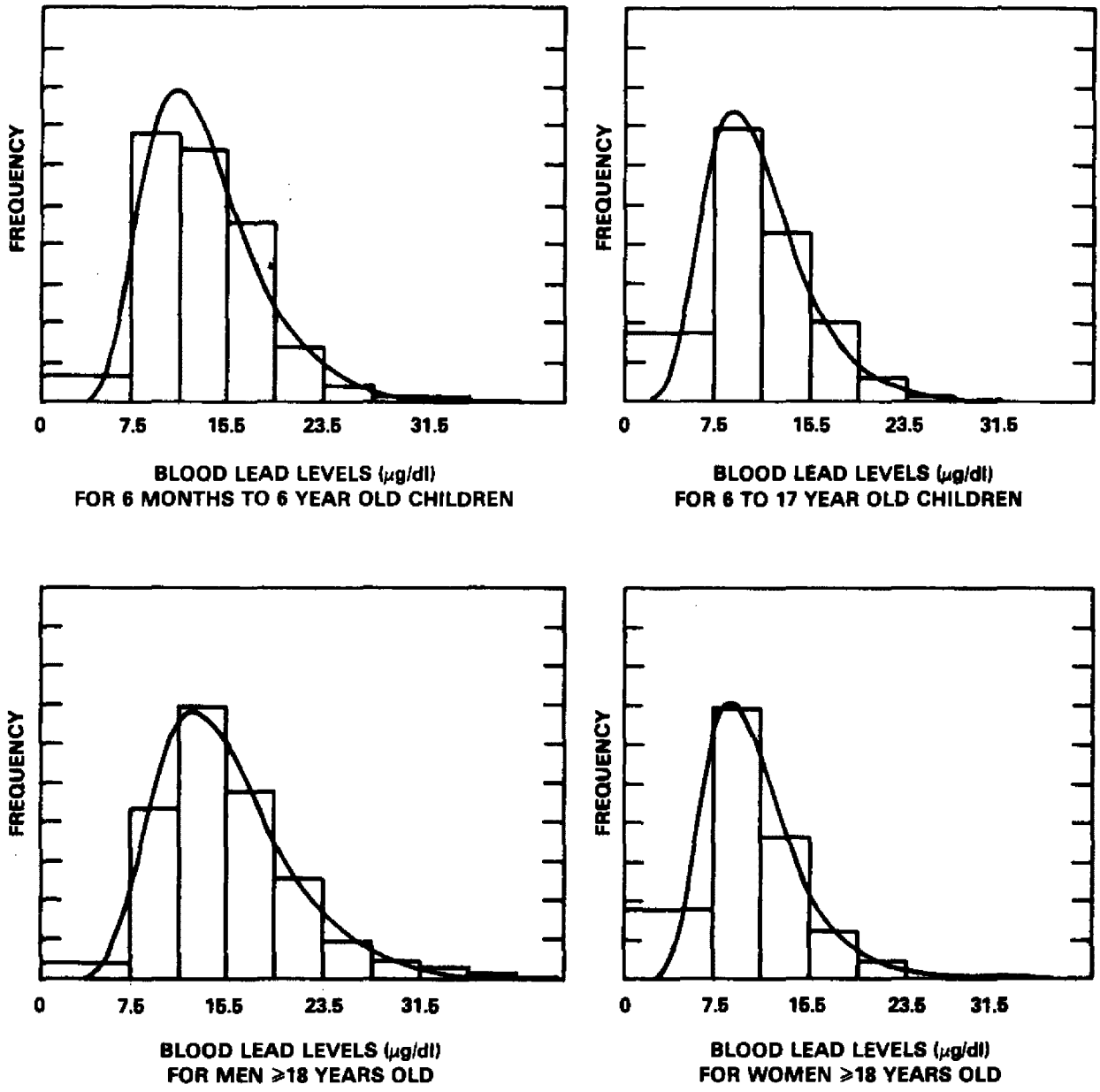

Figure 11-8. Histograms of blood lead levels with fitted lognormal curves for the NHANES II study. All subgroups are white, non-SMSA residents with family incomes greater than $6000.

TABLE 11-11. ESTIMATED MEAN SQUARE ERRORS RESULTING FROM ANALYSIS OF VARIANCE ON VARIOUS SUBPOPULATIONS OF THE NHANES II DATA USING UNWEIGHTED DATA

Age	White, Non SMSA	White, SMSA, not central city	White, central city	Black, central city
0.5 to 6	0.0916 (1.35)*	0.0839 (1.34)	0.1074 (1.39)	0.0978 (1.37)
6 to 18	0.0814 (1.33)	0.0724 (1.31)	0.0790 (1.33)	0.0691 (1.30)
18+, men	0.1155 (1.40)	0.0979 (1.37)	0.1127 (1.40)	0.1125 (1.40)
18+, women	0.1083 (1.39)	0.0977 (1.37)	0.0915 (1.35)	0.0824 (1.33)

Note: Mean square errors are based on the logarithm of the blood lead levels.
*Estimated geometric standard deviations are given in parentheses.

blind pool and from the replicate measurements in the study of Griffin et al. (1975). The overall estimate of analytical variation for the NHANES II study was 0.02083.

Analytical variation causes a certain amount of misclassification when estimates of the percent of individuals above or below a given threshold are made. This is because the true value of a person's blood lead could be below the threshold, but the contribution from analytical variation may push the observed value over the threshold. The reverse is also possible. These two types of misclassifications do not necessarily balance each other.

Annest et al. (1983) estimated this misclassification rate for several subpopulations in the NHANES II data using a threshold value of 30 μg/dl. In general, the percent truly greater than this threshold was approximately 24 percent less than the prevalence of blood lead levels equal to or greater than 30 μg/dl, estimated from the weighted NHANES II data. This is less than the values predicted by Lucas (1981) which were based on some earlier studies.

11.3.6 Exposure Covariates of Blood Lead Levels in Urban Children

Results obtained from the NHANES II study show that urban children generally have the highest blood lead levels of any non-occupationally exposed population group. Furthermore, black urban children have significantly higher blood lead levels than white urban children. Several studies have been reported in the past few years that look at determinants of blood

lead levels in urban children (Stark et al., 1982; Charney et al., 1980; Hammond et al., 1980; Gilbert et al., 1979).

11.3.6.1 Stark Study. Stark et al. (1982) used a large scale lead screening program in New Haven, Connecticut, during 1974-77 as a means of identifying study subjects. The screening program had blood lead levels on 8289 children ages 1-72 months, that represented about 80 percent of the total city population in that age group. From this initial population, a much smaller subset of children was identified for a detailed environmental exposure study. Using the classifying criteria of residential stability and repeatable blood lead levels (multiple measurements fell into one of three previously defined blood lead concentration categories), a potential study population of 784 was identified. Change of residence following identification and refusal to let sanitarians make inspections resulted in 407 children being dropped; the final study population contained 377 children.

With the exception of dietary lead intake, each child's potential total lead exposure was assessed. Information was obtained on lead in air, house dust, interior and exterior paint and soil near and far from the home. A two percent sample of homes with children having elevated lead levels had tap water lead levels assessed. No water lead levels above the public health service standard of 50 μg/l were found. Socioeconomic variables were also obtained.

For all children in the study, micro blood samples were taken and analyzed for lead by AAS with Delves cup attachment. Blood lead values were found to follow a lognormal distribution. Study results were presented using geometric means and geometric standard deviation. Among the various environmental measurements a number of significant correlation coefficients were observed. However, air lead levels were independent of most of the other environmental variables. Environmental levels of lead did not directly follow socioeconomic status. Most of the children, however, were in the lower socioeconomic groups.

Multiple regression analyses were performed by Stark et al. (1982) and by EPA*. Stark and coworkers derived a log-log model with $R^2 = 0.11$, and no significant effects of race or age were found. EPA fitted a linear exposure model in logarithmic form with results shown in Table 11-12. Significant differences among age groups were noted, with considerably improved predictability ($R^2 = 0.29$, 0.30, 0.14 for ages 0-1, 2-3, and 4-7). Sex was not a significant variable, but race equal black was significant at ages 4-7. Air lead did not significantly improve the fit of the model when other covariates were available, particularly dust, soil, paint and housekeeping quality. However, the range of air lead levels was small (0.7-1.3 $\mu g/m^3$) and some of the inhalation effect may have been confounded with dust and soil ingestion. Seasonal variations were important at all ages.

*NOTE: The term EPA analyses refers to calculations done at EPA. A brief discussion of the methods used is contained in Appendix 11-B; more detailed information is available at EPA upon request.

TABLE 11-12. MULTIPLE REGRESSION MODELS FOR BLOOD LEAD OF CHILDREN IN NEW HAVEN, CONNECTICUT, SEPTEMBER 1974 - FEBRUARY 1977

	Regression Coefficients and Standard Errors		
Age group, years	0-1	2-3	4-7
Summer - Winter	6.33 ± 2.11*	3.28 ± 1.30*	2.43 ± 1.38*
Dust, µg/g	0.00402 ± 0.00170*	0.00182 ± 0.00066*	0.00022 ± 0.00077
Housekeeping Quality	4.38 ± 2.02*	1.75 ± 1.17	-1.61 ± 1.12
Soil near house, µg/g	0.00223 ± 0.00091*	-0.00016 ± 0.00042	0.00060 ± 0.00041
Soil at curb, µg/g	0.00230 ± 0.00190	0.00203 ± 0.00082*	0.00073 ± 0.00079
Paint, child's bedroom	0.0189 ± 0.0162	0.0312 ± 0.0066*	0.0110 ± 0.0064*
Paint outside house	-0.0023 ± 0.0138	0.0200 ± 0.0069*	0.0172 ± 0.0067*
Paint quality	0.89 ± 1.71	3.38 ± 0.96*	4.14 ± 1.15*
Race = Black	2.16 ± 2.05	0.07 ± 1.09	5.81 ± 1.00*
Residual Standard Deviations	0.1299	0.0646	0.1052
Multiple R^2	0.289	0.300	0.143
Sample size (blood samples)	153	334	439

*Significant positive coefficient, one-tailed $p < 0.05$

11.3.6.2 Charney Study. Charney et al. (1980) conducted a case control study of children 1.5 to 6 years of age with highly elevated and non-elevated blood lead levels. Cases and controls were initially identified from the lead screening programs of two Rochester, New York, health facilities. Cases were defined as children who had at least two blood lead determinations between 40 and 70 µg/dl and FEP values greater than 59 µg/dl during a 4-month period. Controls were children who had blood lead levels equal to or less than 29 µg/dl and FEP equal to or less than 59 µg/dl. High level children were selected first and low level children were group matched on age, area of residence, and social class of the family. Home visits were made to gain permission as well as to gather questionnaire and environmental data. Lead analyses of the various environmental samples were done at several different laboratories. No specification was provided regarding the analytical procedures followed.

The matching procedure worked well for age, mother's educational level and employment status. There were more blacks in the high lead group as well as more Medicaid support. These factors were then controlled in the analysis; no differences were noted between the high and

low blood lead groups regarding residence on high traffic density streets (>10,000 vehicles/day) or census tract of residence.

The two groups differed regarding mean house dust lead levels (1265 μg/sample for high and 123 μg/sample for low). Median values also differed, 149 vs. 55 μg/sample. One-third of the children in the low blood lead group had house dust lead samples with more lead than those found in any middle class home previously investigated.

There were considerably greater quantities of lead on the hands of the high blood lead group compared with the low group (mean values were 49 μg/sample and 21 μg/sample, respectively). Hand and house dust lead levels were correlated ($r = 0.25$) but the relationship was not linear. At the low end of the house dust lead values, hand dust was always low but the converse was not true: not every child exposed to high house dust lead had high hand dust levels.

In addition to hand and house dust lead, other factors differentiated the high and low blood lead groups. Although both groups had access to peeling paint in their homes (~2/3), paint lead concentrations exceeding 1 percent were found more frequently in the high as opposed to the low group. Pica (as defined in Chapter Seven) was more prevalent in the high lead group as opposed to the low lead group.

Since the data suggested a multifactorial contribution of lead, a multiple regression analysis was undertaken. The results suggest that hand lead level, house dust lead level, lead in outside soil, and history of pica are very important in explaining the observed variance in blood lead levels.

11.3.6.3 Hammond Study. Hammond et al. (1980) conducted a study of Cincinnati children with the dual purpose of determining whether inner city children with elevated blood lead levels have elevated fecal lead and whether fecal lead correlates with lead-base paint hazard in the home or traffic density as compared with blood lead.

Subjects were recruited primarily to have high blood lead levels. Some comparison children with low blood lead levels were also identified. The three comparison children had to be residentially stable so that their low blood lead levels were reflective of the lead intake of their current environment. The subjects from the inner city were usually from families in extremely depressed socio-economic circumstances.

Stool samples were collected on a daily basis for up to 3 weeks, then analyzed for lead. Fecal lead levels were expressed both as mg/kg day and as mg/m^2 day.

An environmental assessment was made at the home of each child. Paint lead exposure was rated on a three-point scale (high, medium and low) based on paint lead level and integrity of the painted wall. Air lead exposure was assessed by the point scale (high, medium and low) based on traffic density, because there are no major point sources of lead in the Cincinnati area.

Blood samples were collected on an irregular basis but were taken sufficiently often to have at least one sample from a child from every house studied. The blood samples were analyzed for lead by two laboratories that had different histories of performance in the CDC proficiency testing program. All blood lead levels used in the statistical analysis were adjusted to a common base. Because of the variable number of fecal and blood lead levels, the data were analyzed using a nested analysis of variance.

The homes of the children were found to be distributed across the paint and traffic lead exposure categories. Both fecal lead levels and blood lead levels were positively associated with interior paint lead hazard. A marginal association between fecal lead levels and exterior paint hazard was also obtained. Neither fecal lead or blood lead was found to be associated with traffic density; the definition of the high traffic density category, however, began at a low level of traffic flow (7500 cars/day).

Examination of fecal and blood lead levels by sex and race showed that black males had the highest fecal lead excretion rates followed by white males and black females. White females were only represented by two subjects, both of whom had high fecal lead excretion. Blood lead levels were more influenced by race than by sex. The results suggested that children in high and medium paint hazard homes (high = at least 1 surface >0.5 percent Pb, peeling or loose) were probably ingesting paint in some form. This could not be confirmed, however, by finding physical evidence in the stools.

Long term stool collection in a subset of 13 children allowed a more detailed examination of the pattern of fecal lead excretion. Two patterns of elevated fecal lead excretion were noted. The first was a persistent elevation compared with controls; the second was markedly elevated occasional spikes against a normal background.

One family moved from a high hazard home to a low one during the course of the study. This allowed a detailed examination of the speed of deleading of fecal and blood lead level. The fecal levels decreased faster than the blood lead levels. The blood leads were still elevated at the end of the collection.

11.3.6.4 Gilbert Study. Gilbert et al. (1979) studied a population of Hispanic youngsters in Springfield, Massachusetts, in a case control study designed to compare the presence of sources of lead in homes of lead poisoned children and appropriately matched controls. Cases were defined as children having two consecutive blood lead levels greater than 50 µg/dl. Controls were children with blood lead levels less than or equal to 30 µg/dl who had no previous history of lead intoxication and were not siblings of children with blood lead levels greater than 30 µg/dl. Study participants had to be residentially stable for at least 9 months and not have moved into their current home from a lead contaminated one. All blood lead levels were analyzed by Delves cup method of AAS. Cases and controls were matched by age (±3 months),

sex and neighborhood area. The study population consisted of 30 lead intoxication cases and 30 control subjects.

Home visits were undertaken to gather interview information and conduct a home inspection. Painted surfaces were assessed for integrity of the surface and lead content. Lead content was measured by X-ray fluorimetry. A surface was scored as positive if the lead content exceeded 1.2 mg/cm^2. Drinking water lead was assessed for each of the cases and was found to contain less than 50 µg/l, sufficiently low so as not to constitute a hazard. Tap water samples were not collected in the homes of the controls. Soil samples were collected from three sites in the yard and analyzed for lead by X-ray fluorometry.

Cases and controls were compared on environmental lead exposures and interview data using McNemar's test for pair samples. The odds ratio was calculated as an estimator of the relative risk on all comparisons. Statistically significant differences between cases and controls were noted for lead in paint and the presence of loose paint. Large odds ratios (>10) were obtained; there appeared to be little influence of age or sex on the odds ratios.

Significant differences between cases and controls were obtained for both intact and loose paint by individual surfaces within specific living areas of the home. Surfaces accessible to children were significantly associated with lead poisoning status while inaccessible surfaces generally were not. Interestingly, the odds ratios tended to be larger for the intact surface analysis than for the loose paint one.

Median paint lead levels in the homes of cases were substantially higher than those in the homes of controls. The median paint lead for exterior surfaces in cases was about 16-20 mg/cm^2 and about 10 mg/cm^2 for interior surfaces. Control subjects lived in houses in which the paint lead generally was less than 1.2 mg/cm^2 except for some exterior surfaces.

Soil lead was significantly associated with lead poisoning; the median soil lead level for homes of cases was 1430 µg/g, while the median soil lead level for control homes was 440 µg/g.

11.4 STUDIES RELATING EXTERNAL DOSE TO INTERNAL EXPOSURE

The purpose of this section is to assess the importance of environmental exposures in determining the level of lead in human populations. Of prime interest are those studies that yield quantitative estimates of the relationship between air lead exposures and blood lead levels. Related to this question is the evaluation of which environmental sources of airborne lead play a significant role in determining the overall impact of air lead exposures on blood lead levels.

A factor that complicates the analysis presented here is that lead does not remain suspended in the atmosphere but rather falls to the ground, is incorporated into soil, dust, and

water, and enters the food chain over time (see Figure 11-1). Since man is exposed to lead from all of these media, as will be demonstrated below, studies that relate air lead levels to blood lead levels (especially experimental exposure studies) may underestimate the overall impact of airborne lead on blood lead levels. In observational studies, the effects of air lead will thus be confounded with lead exposures from other pathways. The simultaneous presence of lead in multiple environmental media requires the use of multiple variable analysis techniques or surrogate assessment of all other external exposures. Virtually no assessments of simultaneous exposures to all media have been done.

Although no study is ever done perfectly, there are several key factors that are present in good studies relating external exposure to internal exposure of lead:

(1) The study population is well-defined.
(2) There is a good measure of the exposure of each individual.
(3) The response variable (blood lead) is measured with adequate quality control, preferably with replicates.
(4) The statistical analysis model is biologically plausible and is consistent with the data.
(5) The important covariates are either controlled for or measured.

Even studies of considerable importance do not address all of these factors adequately. We have selected as key studies (for discussion below) those which address enough of these factors sufficiently well to establish meaningful relationships.

11.4.1 Air Studies

The studies emphasized in this section are those most relevant to answering the following question: If there is moderate change in average ambient air lead concentrations due to changes in environmental exposure (at or near existing EPA air lead standards), what changes are expected in blood lead levels of individual adults and children in the population? Longitudinal studies in which changes in blood lead can be measured in single individuals as responses to changes in air lead are discussed first. The cross-sectional relationship between blood lead and air lead levels in an exposed population provides a useful but different kind of information, since the population "snapshot" at some point in time does not directly measure changes in blood lead levels or responses to changes in air lead exposure. We have also restricted consideration to those individuals without known excessive occupational or personal exposures (except, perhaps, for some children in the Kellogg/Silver Valley study).

The previously published analyses of relevant studies have not agreed on a single form for the relationship between air lead and blood lead. All of the experimental studies have at least partial individual air lead exposure measures, as does the cross-sectional observational

study of Azar et al. (1975). The 1974 Kellogg/Silver Valley study (Yankel et al., 1977) has also been analyzed using several models. Other population cross-sectional studies have been analyzed by Snee (1981). The most convenient method for summarizing these diverse studies and their several analyses is by use of the blood lead-air lead slope (β), where β measures the change in blood lead that is expected for a unit change in air lead. If determined for individual subjects in a study population, this slope is denoted β_i. If the fitted equation is linear, then β or β_i is the slope of the straight line relationship at any air lead level. If the fitted relationship is nonlinear, then the slope of the relationship measures the expected effect on blood lead of a small change in air lead at some given air lead value and thus will be somewhat different at different air lead levels. It is necessary to compare the slopes of the nonlinear relationships at the same value of air lead or change in air lead. A discussion of the linear, nonlinear and compartment models is in Appendix 11A-B.

Snee (1982b,c) has indicated that inclusion of additional sources of lead exposure improves biological plausibility of the models. It is desirable that these sources be as specific to site, experiment and subject as possible.

11.4.1.1 The Griffin et al. Study. In two separate experiments conducted at the Clinton Correctional Facility in 1971 and 1972, adult male prisoner volunteers were sequestered in a prison hospital unit and exposed to approximately constant levels of lead oxide (average 10.9 $\mu g/m^3$ in the first study and 3.2 $\mu g/m^3$ in the second). Volunteers were exposed in an exposure chamber to an artificially generated aerosol of submicron-sized particles of lead dioxide. All volunteers were introduced into the chamber 2 weeks before the initiation of the exposure; the lead exposures were scheduled to last 16 weeks, although the volunteers could drop out whenever they wished. Twenty-four volunteers, including 6 controls, participated in the 10.9 $\mu g/m^3$ exposure study. Not all volunteers completed the exposure regimen. Blood lead levels were found to stabilize after approximately 12 weeks. Among 8 men exposed to 10.9 $\mu g/m^3$ for at least 60 days, a stabilized mean level of 34.5 ± 5.1 $\mu g/dl$ blood was obtained, as compared with an initial level of 19.4 ± 3.3 $\mu g/dl$. All but two of the 13 men exposed at 3.2 $\mu g/m^3$ for at least 60 days showed increases and an overall stabilized level of 25.6 ± 3.9 $\mu g/dl$ was found, compared with an initial level of 20.5 ± 4.4 $\mu g/dl$. This represented an increase of about 25 percent above the base level.

The aerosols used in this experiment were somewhat less complex chemically, as well as somewhat smaller, than those found in the ambient environment. Griffin et al. (1975), however, pointed out that good agreement was achieved on the basis of the comparison of their observed blood lead levels with those predicted by Goldsmith and Hexter's (1967) equation; that is, $\log_{10}$ blood lead = 1.265 + 0.2433 $\log_{10}$ atmospheric air lead. The average diet content of lead was measured and blood lead levels were observed at 1- or 2-week intervals for

several months. Eight subjects received the maximum 4-month exposure to 10.9 $\mu g/m^3$; nine subjects were exposed for 1 to 3 months. Six subjects had the maximum 4-month exposure to 3.2 $\mu g/m^3$, and eight others had shorter exposures.

Compartmental models have been fitted to these data by O'Flaherty et al. (1982) and by EPA. The basis of these models is that the mass of lead in each of several distinct pools or compartments within the body changes according to a system of coupled first-order linear differential equations with constant fractional transfer rates (Batschelet et al., 1979; Rabinowitz et al., 1976). Such a model predicts that when the lead intake changes from one constant level to another, then the relationship between the mass of lead in each compartment and time with constant intake has a single exponential term.

The subjects at 3.2 $\mu g/m^3$ exhibited a smaller increase in blood lead, with correspondingly less accurate estimates of the parameters. Several of the lead-exposed subjects failed to show an increase.

Figure 11-9 shows a graph of the blood lead levels for the 10.9 $\mu g/m^3$ exposure by length of exposure. Each person's values are individually normalized, and then averaged across

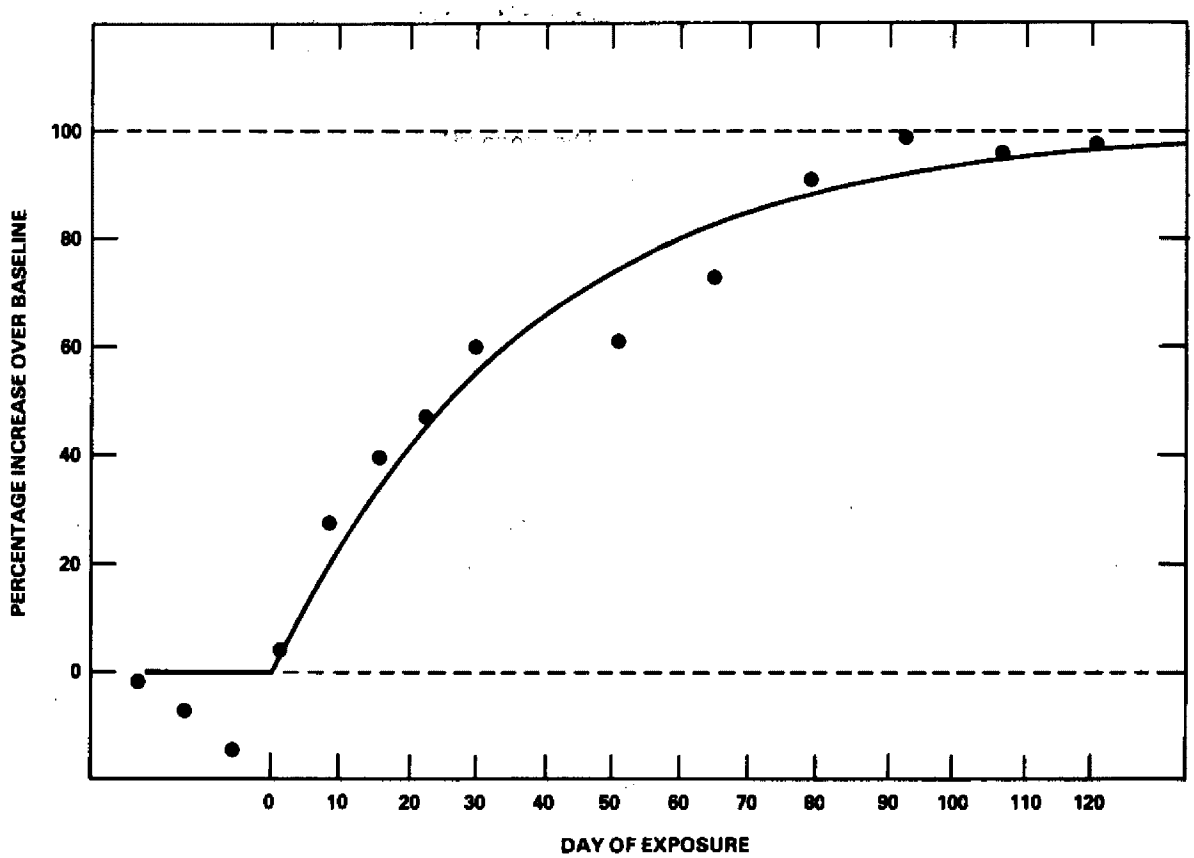

Figure 11-9. Graph of the average normalized increase in blood lead for subjects exposed to 10.9 $\mu g/m^3$ of lead in Griffin et al. study (1975).

subjects for each time period. The smooth curve shows a fitted one-compartment model, assuming pre-exposure equilibrium and constant lead intake during exposure.

EPA has reanalyzed these data using a two-compartment model for two reasons:

(1) Semilogarithmic plots of blood lead vs. time for most subjects showed a two-component exponential decrease of blood lead during the postexposure or washout phase of the experiments. Rabinowitz et al. (1977) show that at least two pools are necessary to model blood lead kinetics accurately. The first pool is tentatively identified with blood and the most labile soft tissues. The second pool probably includes soft tissues and labile bone pools.

(2) Kinetic models are needed to account for the subjects' lead burdens not being in equilibrium at any phase of the experiments.

The pre-exposure decline in Figure 11-9 is apparently real and suggests a low pre-exposure lead intake. The deviation from the fitted curve after about 50 days suggests a possible change in lead intake at that time.

Previously published analyses have not used data for all 43 subjects, particularly for the same six subjects (labeled 15 to 20 in both experiments) who served as controls both years. These subjects establish a baseline for non-inhalation exposures to lead, e.g., in diet and water, and allow an independent assessment of within-subject variability over time. EPA analyzed data for these subjects as well as others who received lead exposures of shorter duration.

The estimated blood lead inhalation slope, β, was calculated for each individual subject according to the formula:

$$\beta = \frac{\text{(Change in intake, } \mu\text{g/day) x (mean residence time in blood, day)}}{\text{(Change in air exposure, } \mu\text{g/m}^3\text{) x (Volume of distribution, dl)}}$$

The mean values of these parameters are given in Tables 11-13 through 11-15. The changes in air exposure were 10.9 - 0.15 = 10.75 $\mu g/m^3$ for 1970-71 and 3.2 - 0.15 = 3.05 $\mu g/m^3$ in 1971-72. Paired sample t-tests of equal means were carried out for the six controls and five subjects with exposure both years, and independent sample t-tests were carried out comparing the remaining 12 subjects the first year and nine different subjects the next year. All standard error estimates include within-subject parameter estimation uncertainties as well as between subject differences. The following are observations.

(1) Non-inhalation lead intake of the control subjects varied substantially during the second experiment at 3.2 $\mu g/m^3$, with clear indication of low intake during the 14-day pre-exposure period (net decrease of blood lead), see Figure 11-10. There was an increase in lead intake (either equilibrium or net increase of blood lead) during the exposure period.

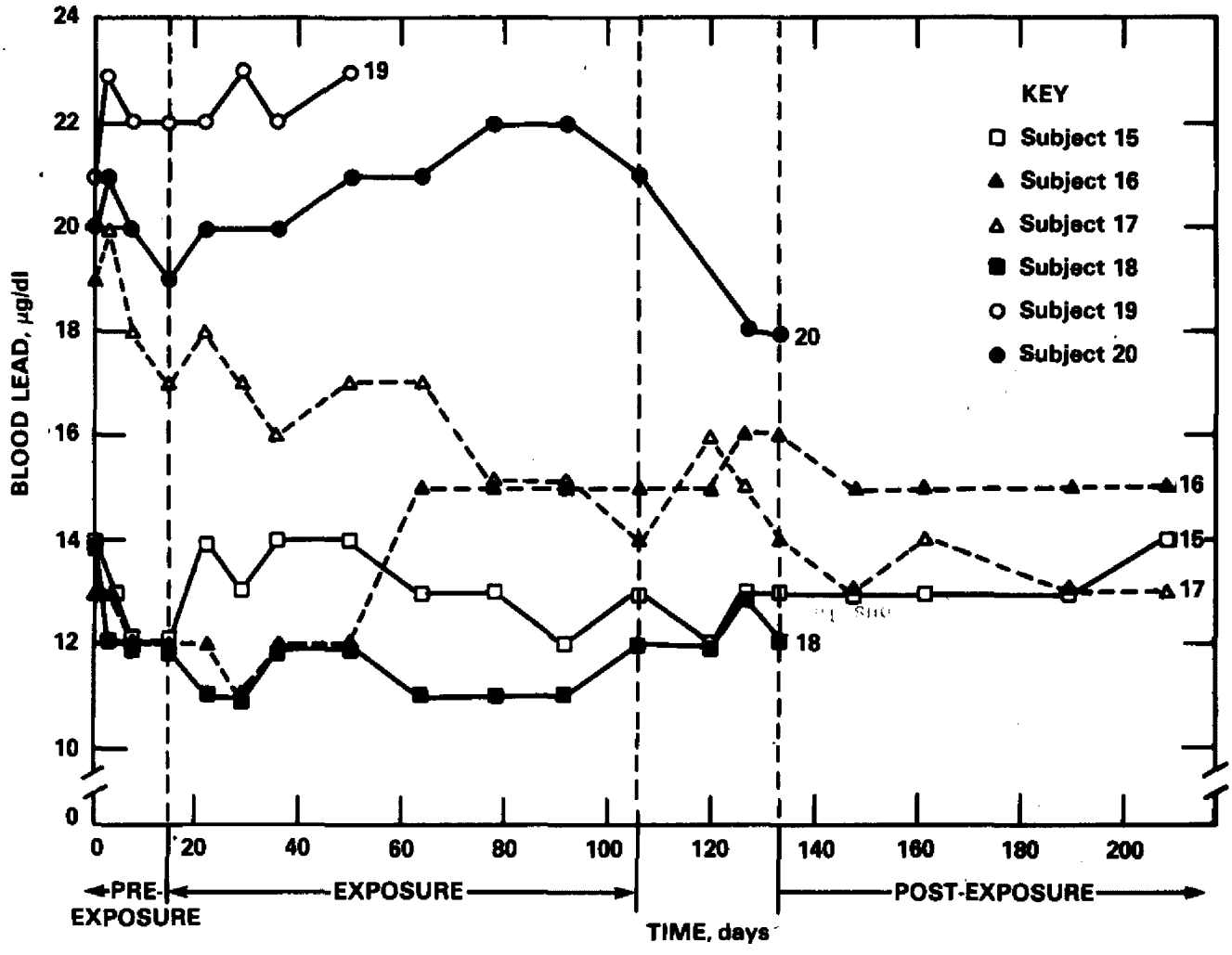

Figure 11-10. Control subjects in Griffin experiment at 3.2 µg/m³.

TABLE 11-13. GRIFFIN EXPERIMENTS - SUBJECTS EXPOSED TO AIR LEAD BOTH YEARS

Subject At 3.2	At 10.9	Mean Residence Time, d. At 3.2	At 10.9	Change in Intake, Post-Pre-exposure, μg/d* At 3.2	At 10.9	Inhalation slope, μg/dℓ per μg/m³* At 3.2	At 10.9
1	3	42.1 ± 17.4	55.2 ± 27.2	-4.4 ± 13.8	-3.0 ± 12.2	0.92 ± 1.94	1.09 ± 0.80
2	13	47.6 ± 21.4	38.4 ± 14.5	3.1 ± 14.1	3.8 ± 14.6	3.95 ± 3.44	1.27 ± 0.79
3	14	48.0 ± 21.7	40.1 ± 15.8	3.3 ± 13.1	11.6 ± 13.4	2.50 ± 2.20	1.88 ± 1.03
4	7	42.5 ± 17.6	50.1 ± 22.5	12.0 ± 14.2	5.1 ± 13.6	3.36 ± 2.49	1.57 ± 0.99
5	4	43.6 ± 18.2	35.9 ± 12.8	0.6 ± 19.3	-9.5 ± 14.3	3.76 ± 2.93	1.29 ± 0.68
Mean		44.7 ± 8.7	43.9 ± 9.4	2.9 ± 7.2	1.6 ± 7.1	2.90 ± 1.31	1.42 ± 0.41
Mean w/o subject 1 at 3.2						3.39 ± 1.44	

*Assumed volume of blood pool is 75 dl.

TABLE 11-14. GRIFFIN EXPERIMENTS - SUBJECTS EXPOSED TO AIR LEAD BOTH YEARS

Subject At 3.2	Mean Residence Time, d. At 3.2	At 10.9	Change in Intake, Post-Pre-exposure, μg/d* At 3.2	At 10.9	Inhalation slope, μg/dℓ per μg/m³* At 3.2	At 10.9
15	28.6 ± 10.4	38.3 ± 21.8	18.6 ± 11.3	-	1.76 ± 1.17	-0.16 ± 0.46
16	36.2 ± 14.6	35.2 ± 16.8	5.0 ± 11.6	4.8 ± 11.8	1.57 ± 1.31	0.14 ± 0.35
17	33.5 ± 14.0	44.2 ± 20.7	7.9 ± 12.1	-8.6 ± 13.5	1.25 ± 1.43	-0.75 ± 0.68
18	34.4 ± 15.7	36.3 ± 18.2	-	2.1 ± 12.1	0.67 ± 1.11	0.09 ± 0.38
19	36.8 ± 19.6	49.1 ± 27.3	-	-3.1 ± 15.6	0.73 ± 2.82	-0.25 ± 0.73
20	34.0 ± 17.8	47.5 ± 24.0	-	-7.2 ± 14.5	2.90 ± 2.46	-0.29 ± 0.70
Mean ± s.e.m.	34.6 ± 6.5	41.8 ± 9.2	10.5 ± 7.9	-2.4 ± 6.6	1.48 ± 0.84	-0.20 ± 0.27

*Assumed volume of blood pool is 75 dℓ.

TABLE 11-15. GRIFFIN EXPERIMENT - SUBJECTS EXPOSED TO AIR LEAD ONE YEAR ONLY

Subject	At 3.2 (second year only) Time, d.	Intake Change µg/d.	Slope	Subject	At 10.9 (first year only) Time, d.	Intake Difference, µg/d	Slope
6	49.4 ± 26.1	3.9 ± 20.1	0.52 ± 3.29	1	35.3 ± 15.4	5.2 ± 20.0	2.17 ± 1.22
7	34.6 ± 11.9	7.0 ± 15.6	4.35 ± 2.48	2	32.6 ± 13.9	8.2 ± 19.7	1.57 ± 0.95
8	38.0 ± 15.2	9.4 ± 15.6	3.33 ± 2.33	5	25.7 ± 9.3	3.0 ± 18.6	1.08 ± 0.62
9	29.7 ± 9.7	3.3 ± 14.8	3.26 ± 1.59	6	45.5 ± 17.5	-6.4 ± 12.4	1.42 ± 0.76
10	40.4 ± 16.9	5.7 ± 13.9	2.08 ± 1.95	8	52.0 ± 22.3	1.5 ± 12.9	1.90 ± 1.05
11	37.5 ± 15.3	-	3.93 ± 2.50	9	38.1 ± 14.1	7.2 ± 13.7	1.67 ± 0.84
12	43.3 ± 17.3	7.4 ± 14.6	4.62 ± 2.81	10	36.9 ± 15.8	-3.9 ± 22.5	0.65 ± 1.06
14	37.9 ± 14.7	-1.4 ± 16.6	3.32 ± 2.25	11	30.1 ± 14.3	10.3 ± 15.9	1.36 ± 1.05
21	36.8 ± 15.6	-7.7 ± 22.5	2.06 ± 3.19	12	38.5 ± 15.7	0.5 ± 23.6	2.09 ± 1.39
Mean	38.6 ± 5.8	3.5 ± 6.3	3.05 ± 0.95	21	62.9 ± 37.2	18.6 ± 16.9	1.80 ± 1.40
				23	43.2 ± 15.8	5.2 ± 14.1	2.04 ± 0.97
Mean w/o subject 6			3.37 ± 0.92	24	30.3 ± 8.3	12.6 ± 13.0	1.80 ± 0.65
				Mean	39.3 ± 6.0	5.2 ± 5.4	1.63 ± 0.32

Subjects 16 and 20 had substantial increases, subjects 15 and 19 had moderate increases and subject 18 had no increase in blood lead during exposure. Subject 17 had a marked decline in blood lead, but the rate of decrease was much faster in the pre-exposure period, suggesting an apparent increase of intake during exposure periods even for this subject. These subjects had not apparently achieved equilibrium in either blood or tissue compartments. Even though these subjects were not exposed to air lead, the estimated difference between blood lead intake before and during exposure of the other subjects was used to calculate the apparent inhalation slope at that exposure. The pooled inhalation slope estimated for all six controls (1.48 ± 0.82 s.e.) was significantly positive ($Z = 1.76$, one-tailed $p < 0.05$), as shown in Table 11-16. No explanation for the increased lead intake during the winter of 1971-72 can be advanced at this time, but factors such as changes in diet or changes in resorption of bone lead are likely to have had equal effect on the lead-exposed subjects.

No statistically significant changes in the controls were found during the first experiment at 10.9 $\mu g/m^3$.

(2) Among the controls, the estimated mean residence time in pool 1 was slightly longer for the first year than the second year, 41.8 ± 9.2 days vs. 34.6 ± 6.5 days, but a paired sample Z-test found that the mean difference for the controls (7.2 ± 11.2 days) was not significantly different from zero (see Table 11-17).

(3) Among the five subjects exposed to 10.9 $\mu g/m^3$ the first year and 3.2 $\mu g/m^3$ the second year, the mean residence time in blood was almost identical (43.9 ± 9.4 vs. 44.7 ± 8.7 days).

(4) The average inhalation slope for all 17 subjects exposed to 10.9 $\mu g/m^3$ is 1.77 ± 0.37 when the slope for the controls is subtracted. The corrected inhalation slope for all 14 subjects exposed to 3.2 $\mu g/m^3$ is 1.52 ± 1.12, or 1.90 ± 1.14 without subjects 1 and 6 who were "non-responders." These are not significantly different. The pooled slope estimate for all subjects is 1.75 ± 0.35. The pooled mean residence time for all subjects is 39.9 ± 2.5 days.

Thus, in spite of the large estimation variability at the lower exposure level, the average inhalation slope estimate and blood lead half-life are not significantly different at the two exposure levels. This suggests that blood lead response to small changes in air lead inhalation is approximately linear at typical ambient levels.

11.4.1.2 The Rabinowitz et al. Study. The use of stable lead isotopes avoids many of the difficulties encountered in the analysis of whole blood lead levels in experimental studies. Five adult male volunteers were housed in the metabolic research wards of the Sepulveda and Wadsworth VA hospitals in Los Angeles for extended periods (Rabinowitz et al., 1974; 1976; 1977). For much of the time they were given low-lead diets with controlled lead content, supplemented by tracer lead salts at different times.

TABLE 11-16. INHALATION SLOPE ESTIMATES

Group	At 3.2 $\mu g/m^3$	At 10.9 $\mu g/m^3$
Controls	1.48 ± 0.82	-0.20 ± 0.27
All exposed	3.00 ± 0.76	1.57 ± 0.26
Difference (Exposed-controls)	1.52 ± 1.12	1.77 ± 0.37
Without subjects 1, 6	3.38 ± 0.79	
Difference (Exposed w/o 1,6 - control)	1.90 ± 1.14	
Pooled: (all subjects)	1.75 ± 0.35	
(without subjects 1,6)	1.78 ± 0.35	

TABLE 11-17. MEAN RESIDENCE TIME IN BLOOD

	3.2 $\mu g/m^3$ Experiment	10.9 $\mu g/m^3$ Experiment
Control	34.6 ± 6.5 days	41.8 ± 9.2 days
Exposed	40.8 ± 4.4 days	40.6 ± 3.6 days

Four subjects were initially observed in the ward for several weeks. Each subject was in the semi-controlled ward about 14 hours per day and was allowed outside for 10 hours per day, allowing the blood lead concentration to stabilize.

Subjects B, D and E then spent 22 to 24 hours per day for 40, 25 and 50 days, respectively, in a low lead room with total particulate and vapor lead concentrations that were much lower than in the metabolic wards or outside (see Table 11-18). The subjects were thereafter exposed to Los Angeles air with much higher air lead concentrations than in the ward.

The calculated changes in lead intake upon entering and leaving the low-lead chamber are shown in Table 11-19. These were based on the assumption that the change in total blood lead was proportional to the change in tracer lead. The change in calculated air lead intakes (other than cigarettes) due to removal to the clean room were also calculated independently by the lead balance and labeled tracer methods (Rabinowitz et al., 1976) and are consistent with these direct estimates.

TABLE 11-18. AIR LEAD CONCENTRATIONS ($\mu g/m^3$) FOR TWO SUBJECTS IN THE RABINOWITZ STUDIES

		Average	Range
Subject A	outside (Sepulveda VA)	1.8	(1.2-2.4)
	inside (Sepulveda VA, airconditioned without filter)	1.5	(1.0-2.7)
	inside (Wadsworth VA, open air room)	2.1	(1.8-2.6)
Subject B	(Wadsworth VA)		
	outside	2.0	(1.6-2.4)
	in room (air conditioner with filter, no purifier)	0.91	(0.4-2.1)
	in room (with purifiers, "clean air")	0.072	(0.062-0.087)
	open-air room	1.9	(1.8-1.9)
	organic vapor lead		
	outside	0.10	-
	"clean air"	0.05	-

* 5-20 days exposure for each particulate lead filter

Rabinowitz and coworkers assumed that the amount of lead in compartments within the body evolved as a coupled system of first-order linear differential equations with constant fractional transfer rates. This compartmental model was fitted to the data. This method of analysis is described in Appendix 11A.

Blood lead levels calculated from the three compartment model adequately predicted the observed blood lead levels over periods of several hundred days. There was no evidence to suggest homeostasis or other mechanisms of lead metabolism not included in the model. There was some indication (Rabinowitz et al., 1976) that gut absorption may vary from time to time.

The calculated volumes of the pool with blood lead (Table 11-19) are much larger than the body mass of blood (about 7 percent of body weight, estimated respectively as 4.9, 6.3, 6.3, 4.6 and 6.3 kg for subjects A-E). The blood lead compartment must include a substantial mass of other tissue.

TABLE 11-19. ESTIMATES OF INHALATION SLOPE FOR RABINOWITZ STUDIES

Subject	Changes in Intake*, µg/day	Volume**, kg	Residence† Time, days	Changes in Air Lead†† µg/m³	Inhalation† Slope µg/dℓ per µg/m³	Maximum++ Slope
A	17 ± 5*	7.4 ± 0.6	34 ± 5	2.5††	2.98 ± 1.06	4.38 ± 1.55
B	16 ± 3	10.0 ± 0.8	40 ± 5	2.0	3.56 ± 0.93	5.88 ± 1.54
C	15 ± 5*	10.1 ± 1**	37 ± 5	2.2††	2.67 ± 1.04	4.16 ± 1.62
D	9 ± 2	9.9 ± 1.2	40 ± 5	2.0	2.02 ± 0.60	3.34 ± 0.99
E	12 ± 2	11.3 ± 1.4	27 ± 5	2.0	1.59 ± 0.47	2.63 ± 0.78

*From (Rabinowitz et al., 1977) Table VI. Reduced intake by low-lead method for subjects B, D, E, tracer method for A, balance method for C. Standard error for C is assumed by EPA to be same as A.

**From (Rabinowitz et al., 1976) Table II. EPA has assumed standard error with coefficient of variation same as that for quantity of tracer absorbed in Table VI, except for subject C.

†Estimates from (Rabinowitz et al., 1976) Table II. Standard error estimate from combined sample.

††See text, For A and C, estimated from average exposure. For B, D, E reduced by 0.2 µg/m³ for clean room exposure. Coefficient of variation assumed to be 10%.

+Assumed density of blood 1.058 g/cm³.

++Assuming outside air exposure is 2.1 µg/m³ rather than 4 µg/m³ for 10 hours.

The mean residence time in blood in Table 11-19 includes both loss of lead from blood to urine and transfer of a fraction of blood lead to other tissue pools. This parameter reflects the speed with which blood lead concentrations approach a new quasi-equilibrium level. Many years may be needed before approaching a genuine equilibrium level that includes lead that can be mobilized from bones.

One of the greatest difficulties in using these experiments is that the air lead exposures of the subjects were not measured directly, either by personal monitors or by restricting the subjects to the metabolic wards. The times when the subjects were allowed outside the wards included possible exposures to ground floor and street level air, whereas the outside air lead monitor was mounted outside the third-floor window of the ward. The VA hospitals are not far from major streets and the subjects' street level exposures could have been much higher than those measured at about 10 m elevation (see Section 7.2.1.3). Some estimated ratios between air concentrations at elevated and street level sites are given in Table 7.6.

A second complication is that the inside ward value of 0.97 µg/m³ (Rabinowitz et al., 1977) used for subject B may be appropriate for the Wadsworth VA hospital, but not for subject

A in the Sepulveda VA hospital (see Table 11-18). The change in air lead values shown in Table 11-19 is thus nominal, and is likely to have systematic inaccuracies much larger than the nominal 10 percent coefficients of variation stated. The assumption is that for subjects B, D and E, the exposure to street level air for 10 hours per day was twice as large as the measured roof level air, i.e., 4 $\mu g/m^3$; and the remaining 14 hours per day was at the ward level of 0.97 $\mu g/m^3$; thus the time-averaged level was (10 x 4 + 14 x 0.97)/24 = 2.23 $\mu g/m^3$. The average controlled exposure during the "clean room" part of the experiment was 23, 22 and 24 hours respectively for subjects B, D, E; thus averaged exposures were 0.19, 0.28, and 0.12 $\mu g/m^3$, and reductions in exposure were about 2.0 $\mu g/m^3$. This value is used to calculate the slope. For subject A, the total intake due to respired air is the assumed indoor average of 1.5 $\mu g/m^3$ for the Sepulveda VA hospital, combining indoor and outdoor levels (10 x 4 + 14 x 1.5)/24 = 2.54 $\mu g/m^3$. For subject C we use the Wadsworth average. Apart from uncertainties in the air lead concentration, the inhalation slope estimates for Rabinowitz's subjects have less internal uncertainty than those calculated for subjects in Griffin's experiment.

The inhalation slopes thus calculated are the lowest that can be reasonably derived from this experiment, since the largest plausible air lead concentrations have been assumed. The third-floor air monitor average of 2.1 $\mu g/m^3$ is a plausible minimum exposure, leading to the higher plausible maximum inhalation slopes in the last column of Table 11-19. These are based on the assumption that the time-averaged air lead exposure is smaller by 10x(4-2.1)/24 = 0.79 $\mu g/m^3$ than assumed previously. It is also possible that some of this difference can be attributed to dust ingestion while outside the metabolic ward.

11.4.1.3 The Chamberlain et al. Study. A series of investigations were carried out by A.C. Chamberlain et al. (1975a,b; 1978) at the U.K. Atomic Energy Research Establishment in Harwell, England. The studies included exposure of up to 10 volunteer subjects to inhaled, ingested and injected lead in various physical forms. The inhalation exposures included laboratory inhalation of lead aerosols generated in a wind tunnel, or box, of various particle sizes and chemical compositions (lead oxide and lead nitrate). Venous blood samples were taken at several times after inhalation of ^{203}Pb. Three subjects also breathed natural highway exhaust fumes at various locations for times up to about 4.5 hours.

The natural respiratory cycles in the experiments varied from 5.7 to 17.6 seconds (4 to 11 breaths per minute) and tidal volumes from 1.6 to 2.3 liters. Lung deposition of lead-bearing particles depended strongly on particle size and composition, with natural exhaust particles being more efficiently retained by the lung (30 to 50 percent) than were the chemical compounds (20 to 40 percent).

The clearance of lead from the lungs was an extended process over time and depended on particle size and composition, leaving only about 1 percent of the fine wind tunnel aerosols

in the lung after 100 hours, but about 10 percent of the carbonaceous exhaust aerosols. The ^{203}Pb isotope reached a peak blood level about 30 hours after inhalation, the blood level then representing about 60 percent of the initial lung burden.

A substantial fraction of the lead deposited in the lung appears to be unavailable to the blood pool in the short term, possibly due to rapid transport to and retention in other tissues including skeletal tissues. In long term balance studies, some of this lead in deep tissue compartment would return to the blood compartment.

Lead kinetics were also studied by use of injected and ingested tracers, which suggested that in the short term, the mean residence time of lead in blood could be calculated from a one-pool model analysis.

Chamberlain et al. (1978) extrapolated these high level, short term exposures to longer term ones. The following formula and data were used to calculate a blood-to-air level ratio:

$$\beta = \frac{[T_{1/2}]\ [\%\ \text{Deposition}]\ [\%\ \text{Absorption}]\ [\text{Daily ventilation}]}{[\text{Blood volume}]\ [0.693]}$$

where: $T_{1/2}$ = biological half life

With an estimated value of $T_{1/2}$ = 18 days (mean residence time $T_{1/2}/0.693$ = 26 days), with 50 percent for deposition in lung for ordinary urban dwellers, and 55 percent of the lung lead retained in the blood lead compartment (all based on Chamberlain's experiments), with an assumed ventilation of 20 m^3/day over blood volume 5400 ml (Table 10.20 in Chamberlain et al., 1978), then

$$\beta = \frac{26\ \text{day} \times 0.50 \times 0.55 \times 20\ m^3/\text{day}}{54\ \text{dl}} = 2.7\ m^3/\text{dl}$$

This value of β could vary for the following reasons,

1. The absroption from lung to blood used here, 0.55, refers to short term kinetics. In the long term, little lead is lost through biliary or pancreatic secretions, nails, hair and sweat, so that most of the body lead is available to the blood pool even if stored in the skeleton from which it may be resorbed. Chamberlain suggests an empirical correction to 0.55 X 1.3 = 0.715 absorption.

2. The mean residence time, 26 days, is shorter than in Rabinowitz's subjects, and the blood volume is less, 54 dl. It is possible that in the Rabinowitz study,

the mean times are longer and the blood pool size (100 dl) is larger than here because Rabinowitz et al. included relatively less labile tissues such as kidney and liver in the pool. Assuming 40 days mean residence time and 100 dl blood volume the slope can be recalculated,

$$\beta = \frac{40 \text{ d} \times 0.50 \times 0.55 \times 20 \text{ m}^3/\text{d}}{100 \text{ dl}} = 2.2 \text{ m}^3/\text{dl}$$

3. The breathing rate could be much less, for inactive people.

11.4.1.4 The Kehoe Study. Between 1950 and 1971, Professor R. A. Kehoe exposed 12 subjects to various levels of air lead under a wide variety of conditions. Four earlier subjects had received oral Pb during 1937-45. The inhalation experiments were carried out in an inhalation chamber at the University of Cincinnati, in which the subjects spent varying daily time periods over extended intervals. The duration was typically 112 days for each exposure level in the inhalation studies, at the end of this period it was assumed the blood lead concentration had reached a near equilibrium level. The experiments are described by Kehoe (1961a,b,c) and the data and their analyses by Gross (1981) and Hammond et al. (1981). The studies most relevant to this document are those in which only particles of lead sesquioxide aerosols in the submicron range were used, so that there was at least one air lead exposure (other than control) for which the time-averaged air lead concentration did not exceed 10 $\mu g/m^3$. Only six subjects met these criteria: LD (1960-63), JOS (1960-63), NK (1963-66), SS (1963-68), HR (1966-67) and DH (1967-69). Subject DH had a rather high initial lead concentration (30 $\mu g/dl$) that fell during the course of the experiment to 28 $\mu g/dl$; apparently daily detention in the inhalation chamber altered DH's normal pattern of lead exposure to one of lesser total exposure. The Kehoe studies did not measure non-experimental airborne lead exposures, and did not measure lead exposures during "off" periods. Subject HR received three exposure levels from 2.4 to 7.5 $\mu g/m^3$, subject NK seven exposure levels from 0.6 to 4.2 $\mu g/m^3$ and subjects SS 13 exposure levels from 0.6 to 7.2 $\mu g/m^3$. LD and JOS were each exposed to about 9, 19, 27 and 36 $\mu g/m^3$ during sequential periods of 109-113 days.

A great deal of data on lead content in blood, feces, urine and diet were obtained in these studies and are exhibited graphically in Gross (1979) (see Figure 11-11). Apart from the quasi-equilibrium blood lead values and balances reported in Gross (1979; 1981), there has been little use of these data to study the uptake and distribution kinetics of lead in man. EPA analyses used only the summary data in Gross (1981).

Data from Gross (1981) were fitted by least squares linear and quadratic regression models. The quadratic models were not significantly better than the linear model except for

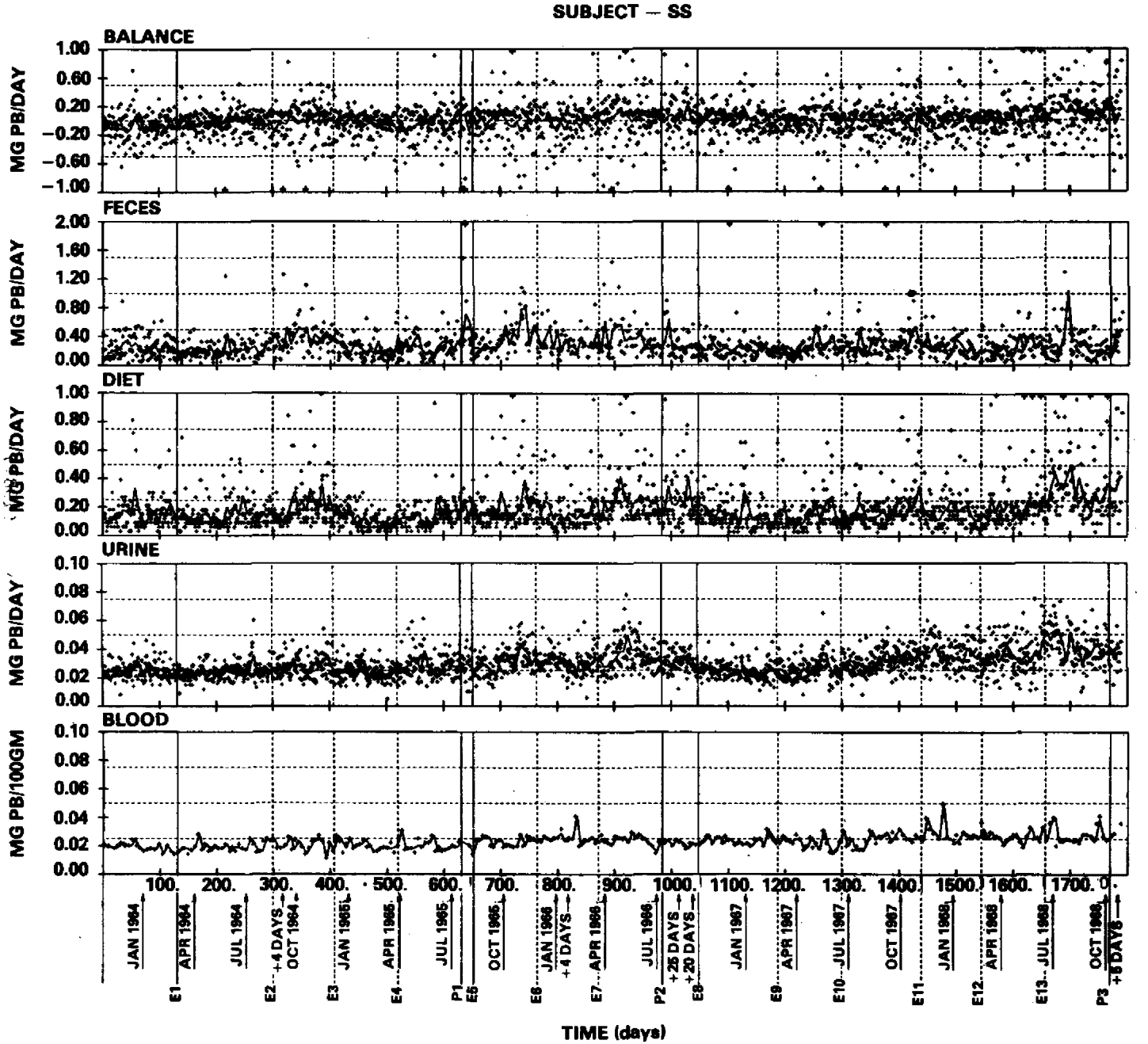

Figure 11-11. Data plots for individual subjects with time for kehoe data as presented by Gross.

subjects LD and JOS, who were exposed to air levels above 10 μg/m^3. The linear terms predominate in all models for air lead concentrations below 10 μg/m^3 and are reported in Table 11-20. These data represent most of the available experimental evidence in the higher range of ambient exposure levels, approximately 3 to 10 μg/m^3.

Data for the four subjects with statistically significant relationships are shown in Figure 11-12, along with the fitted regression curve and its 95 percent confidence band.

TABLE 11-20. LINEAR SLOPE FOR BLOOD LEAD VS. AIR LEAD AT LOW AIR LEAD EXPOSURES IN KEHOE'S SUBJECTS

SUBJECT	LINEAR SLOPES β, m^3/dl, ± s.e. LINEAR MODEL	QUADRATIC MODEL	RANGE AIR*	BLOOD
DH[a]	-0.34 ± 0.28	0.14 ± 1.25	5.6 - 8.8	26 - 31
HR[a]	0.70 ± 0.46	0.20 ± 2.14	2.4 - 7.5	21 - 27
JOS[b]	0.67 ± 0.07	1.01 ± 0.19	9.4 - 35.7	21 - 46
LD[b]	0.64 ± 0.11	1.29 ± 0.06	9.3 - 35.9	18 - 41
NK[c]	2.60 ± 0.32	1.55 ± 1.28	0.6 - 4.0	20 - 30
SS[c]	1.31 ± 0.20	1.16 ± 0.78	0.6 - 7.2	18 - 29

*Also control = 0

[a]No statistically significant relationship between air and blood lead.

[b]High exposures. Use linear slope from quadratic model.

[c]Low exposures. Use linear slope from linear model.

11.4.1.5 The Azar et al. Study. Thirty adult male subjects were obtained from each of five groups: 1) Philadelphia cab drivers; 2) DuPont employees in Starke, Florida; 3) DuPont employees in Barksdale, Wisconsin; 4) Los Angeles cab drivers; and 5) Los Angeles office workers (Azar et al., 1975). Subjects carried air lead monitors in their automobiles and in their breathing zones at home and work. Personal variables (age, smoking habits, water samples) were obtained from all subjects, except for water samples from Philadelphia cab drivers. Blood lead, ALAD urine lead and other variables were measured. From two to eight blood samples were obtained from each subject during the air monitoring phase. Blood lead determinations were done in duplicate. Table 11-21 presents the geometric means for air lead and blood lead for the five groups. The geometric means were calculated by EPA from the raw data presented in the authors' report (Azar et al., 1975).

The Azar study has played an important role in setting standards because of the care used in measuring air lead in the subjects' breathing zone. Blood lead levels change in response to air lead levels, with typical time constants of 20 to 60 days. One must assume that the subjects' lead exposures during preceding months had been reasonably similar to those during

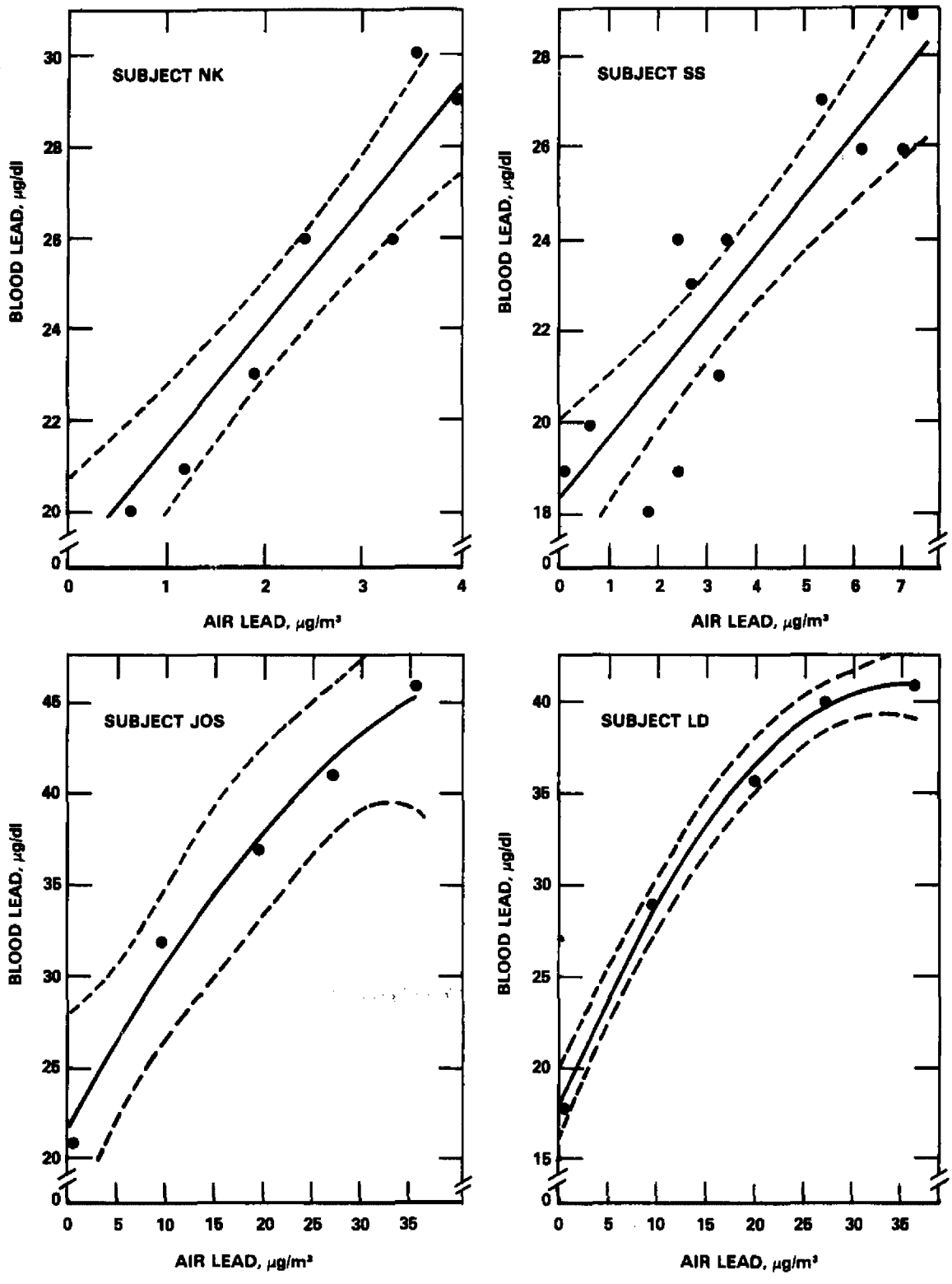

Figure 11-12. Blood level vs. air lead relationships for kehoe inhalation studies: linear relation for low exposures, quadratic for high exposures, with 95% confidence bands

TABLE 11-21. GEOMETRIC MEAN AIR AND BLOOD LEAD LEVELS (μg/100 g) FOR FIVE CITY-OCCUPATION GROUPS (DATA CALCULATED BY EPA)

Group	Geometric mean air lead, μg/m³	GSD	Geometric mean blood lead, μg/100 g	GSD	Sample size	Code
Cab drivers Philadelphia, PA	2.59	1.16	22.1	1.16	30	C_1
Plant employees Starke, FL	0.59	2.04	15.4	1.41	29	C_2
Plant employees Barksdale, WI	0.61	2.39	12.8	1.43	30	C_3
Cabdrivers Los Angeles, CA	6.02	1.18	24.2	1.20	30	C_4
Office workers Los Angeles, CA	2.97	1.29	18.4	1.24	30	C_5

Source: Azar et al. (1975).

the study period. Models have been proposed for these data by Azar et al. (1975), Snee (1981; 1982b) and Hammond et al. (1981) including certain nonlinear models.

Azar et al. (1975) used a log-log model for their analysis of the data. The model included dummy variables, C_1, C_2, C_3, C_4, C_5, which take on the value 1 for subjects in that group and 0 otherwise (see Table 11-21 for the definitions of these dummy variables). The fitted model using natural logarithms was

$$\log(\text{blood Pb}) = 2.951\,C_1 + 2.818\,C_2 + 2.627\,C_3 + 2.910\,C_4 + 2.821\,C_5 + 0.153\log(\text{air Pb})$$

This model gave a residual sum of squares of 9.013, a mean square error of 0.63 (143 degrees of freedom), and a multiple R^2 of 0.502. The air lead coefficient had a standard error of 0.040. The fitted model is nonlinear in air lead, and so the slope depends on both air lead and the intercept. Using an average intercept value of 1.226, the curve has a slope ranging from 10.1 at an air lead level of 0.2 μg/m³ to 0.40 at an air lead level of 9 μg/m³.

Snee (1982b) reanalyzed the same data and fitted the following power function model,

$$\log(\text{blood Pb}) = \log[12.1(\text{air Pb} + 6.00\,C_1 + 1.46\,C_2 + 0.44\,C_3 + 2.23\,C_4 + 6.26\,C_5)^{0.2669}]$$

This model gave a residual sum of squares of 9.101, a mean square error of 0.064 (142 degrees of freedom) and a multiple R^2 of 0.497. Using an average constant value of 3.28, the slope ranges from 1.29 at an air lead of 0.2 to 0.51 at an air lead of 9.

An important extension in the development of models for the data was the inclusion of separate non-air contributions or background exposures for each separate group. The coefficients of the group variables, C_j, in the lead exposure model may be interpreted as measures of total exposure of that group to non-air external sources (cigarettes, food, dust, water) and to endogenous sources (lead stored in skeleton). Water and smoking variables were used to estimate some external sources. (This required deleting another observation for a subject with unusually high water lead.) The effect of endogenous lead was estimated using subject age as a surrogate measure of cumulative exposure, since lead stored in skeleton is known to increase approximately linearly with age, for ages 20 to 60 (Gross et al., 1975; Barry, 1975; Steenhout, 1982) in homogeneous populations.

In order to facilitate comparison with the constant β ratios calculated from the clinical studies, EPA fitted a linear exposure model to the Azar data. The model was fitted on a logarithmic scale to facilitate comparison of goodness of fit with other exposure models and to produce an approximately normal pattern of regression residuals. Neither smoking nor water lead provided significantly better fits to the log (blood lead) measurements after the effect of age was removed.

Age and air lead may be confounded to some extent because the regression coefficient for age may include the effects of prior air lead exposures on skeletal lead buildup. This would have the effect of reducing the estimated apparent slope β.

Geometric mean regressions of blood lead on air lead were calculated by EPA for several assumptions: (i) A linear model analogous to Snee's exposure model, assuming different non-air contributions in blood lead for each of the five subgroups; (ii) linear model in which age of the subject is also used as a surrogate measure of the cumulative body burden of lead that provides an endogenous source of blood lead; (iii) linear model similar to (ii), in which the change of blood lead with age is different in different subgroups, but it is assumed that the non-air contribution is the same in all five groups (as was assumed in the 1977 criteria document); (iv) linear model in which both the non-air background and the change in blood lead

with age may differ by group; and (v) nonlinear model similar to (iv). None of the fitted models are significantly different from each other using statistical tests of hypotheses about parameter subsets in nonlinear regression (Gallant, 1975).

11.4.1.6 Silver Valley/Kellogg, Idaho Study. In 1970, EPA carried out a study of a lead smelter in Kellogg, Idaho (Hammer et al., 1972; U.S. Environmental Protection Agency, 1972). The study was part of a national effort to determine the effects of sulfur dioxide, total suspended particulate and suspended sulfates, singly and in combination with other pollutants, on human health. It focused on mixtures of the sulfur compounds and metals. Although it was demonstrated that children had evidence of lead absorption, insufficient environmental data were reported to allow further quantitative analyses.

In 1974, following the hospitalization of two children from Kellogg with suspected acute lead poisoning, the CDC joined the State of Idaho in a comprehensive study of children in the Silver Valley area of Shoshone County, Idaho, near the Kellogg smelter (Yankel et al., 1977; Landrigan et al., 1976).

The principal source of exposure was a smelter whose records showed that emissions averaged 8.3 metric tons per month from 1955 to 1964 and 11.7 metric tons from 1965 to September 1973. After a September 1973 fire extensively damaged the smelter's main emission filtration facility, emissions averaged 35.3 metric tons from October 1973 to September 1974 (Landrigan et al., 1976). The smelter operated during the fall and winter of 1973-74 with severely limited air pollution control capacity. Beginning in 1971, ambient concentrations of lead in the vicinity of the smelter were determined from particulate matter collected by Hi-Vol air samples. Data indicated that monthly average levels measured in 1974 (Figure 11-13) were three to four times the levels measured in 1971 (von Lindern and Yankel, 1976). Individual exposures of study participants to lead in the air were estimated by interpolation from these data. Air lead exposures ranged from 1.5 $\mu g/m^3$ to 30 $\mu g/m^3$ monthly average (see Figure 11-13). Soil concentrations were as high as 24,000 µg/g and averaged 7000 µg/g within one mile of the smelter. House dusts were found to contain as much as 140,000 µg/g and averaged 11,000 µg/g in homes within one mile of the complex.

The study was initiated in May of 1974 and the blood samples were collected in August 1974 from children 1 to 9 years old in a door-to-door survey (greater than 90 percent participation). Social, family and medical histories were conducted by interview. Paint, house dust, yard and garden soils, grass, and garden vegetable samples were collected. At that time, 385 of the 919 children examined (41.9 percent) had blood lead levels in excess of 40 µg/dl, 41 children (4.5 percent) had levels greater than 80 µg/dl. All but 2 of the 172 children living within 1.6 km of the smelter had levels greater than or equal to 40 µg/dl. Those two children had moved into the area less than six months earlier and had blood lead

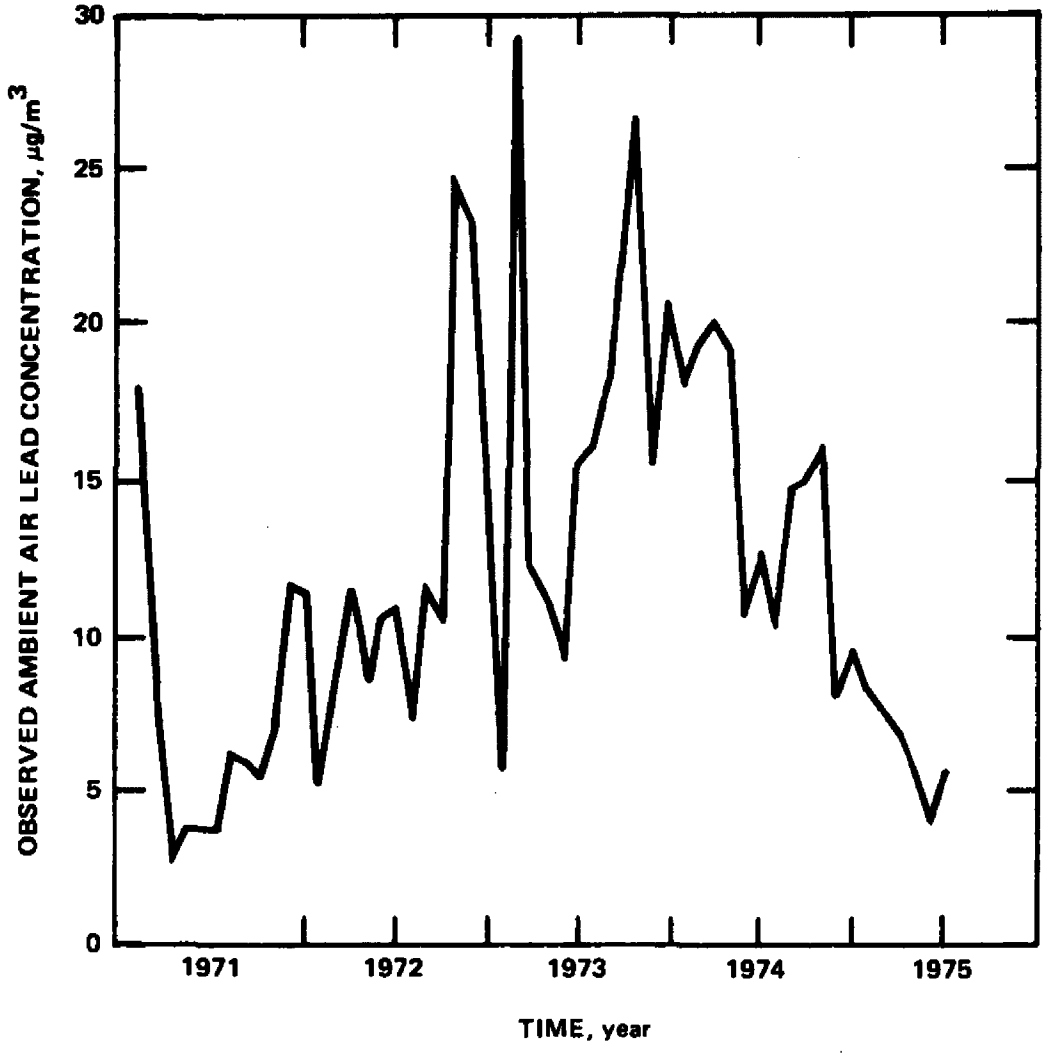

Figure 11-13. Monthly ambient air lead concentrations in Kellogg, Idaho, 1971 through 1975.

levels greater than 35 μg/dl. Both the mean blood lead concentration and the number of children classified as exhibiting excess absorption, decreased with distance from the smelter (Table 11-22). Blood lead levels were consistently higher in 2- to 3-year-old children than they were in other age groups (Table 11-23). A significant negative relationship between blood lead level and hematocrit value was found. Seven of the 41 children (17 percent) with blood lead levels greater than 80 μg/dl were diagnosed as being anemic on the basis of hematocrit less than 33 percent, whereas only 16 of 1006 children (1.6 percent) with blood lead levels less than 80 μg/dl were so diagnosed. Although no overt disease was observed in children with higher lead intake, differences were found in nerve conduction velocity. Details of this finding are discussed in chapter 12.

Yankel et al. (1977) fitted the data to the following model:

$$\ln(\text{blood lead}) = 3.1 + 0.041\ \text{air lead} + 2.1 \times 10^{-5}\ \text{soil lead} + 0.087\ \text{dustiness} - 0.018\ \text{age} + 0.024\ \text{occupation}$$

where air lead was in $\mu g/m^3$; soil lead was in μg/g; dustiness was 1, 2 or 3; age was in years; and occupation was a Hollingshead index. The analysis included 879 subjects, had a multiple R^2 of 0.622 and a residual standard deviation of 0.269 (geometric standard deviation of 1.31).

Walter et al. (1980) used a similar model to examine age specific differences of the regression coefficients for the different variables. Those coefficients are summarized in Table 11-24. The variable that was most significant overall was air lead; its coefficient was approximately the same for all ages, corresponding to a change in blood lead of about 1 μg/dl per unit increase of air lead (in $\mu g/m^3$) at an air exposure of 1 $\mu g/m^3$ and about 2.4 μg/dl per unit increase in air at an air exposure of 22 $\mu g/m^3$.

The next most important variable that attained significance at a variety of ages was the household dustiness level (coded as low = 0, medium = 1 or high = 2), showing a declining effect with age and being significant for ages 1 to 4 years. This suggested age-related hygiene behavior and a picture of diminishing home orientation as the child develops. For ages 1 to 4 years, the coefficient indicates the child in a home with a "medium" dust level would have a blood lead level ~ 10 percent higher than a child in a home with a "low" dust level, other factors being comparable.

The coefficients for soil lead-blood lead relationships exhibited a fairly regular pattern, being highly significant ($p < 0.01$) for ages 3 to 6 years, and significant ($p < 0.05$) at ages 2 to 6 years. The maximum coefficient (at age 6) indicates a 4 percent increase in blood lead per 1000 μg/g increase in soil lead.

TABLE 11-22. GEOMETRIC MEAN BLOOD LEAD LEVELS BY AREA COMPARED WITH ESTIMATED AIR-LEAD LEVELS FOR 1- TO 9-YEAR-OLD CHILDREN LIVING NEAR IDAHO SMELTER. (GEOMETRIC STANDARD DEVIATIONS, SAMPLE SIZES AND DISTANCES FROM SMELTER ARE ALSO GIVEN)[a]

Area	Geometric mean blood lead, µg/dl	GSD	Sample size	% blood lead >40µg/dl	Estimated air lead, µg/m^3	Distance from smelter, km
1	65.9	1.30	170	98.9	18.0	0- 1.6
2	47.7	1.32	192	72.6	14.0	1.6- 4.0
3	33.8	1.25	174	21.4	6.7	4.0-10.0
4	32.2	1.29	156	17.8	3.1	10.0-24.0
5	27.5	1.30	188	8.8	1.5	24.0-32.0
6	21.2	1.29	90	1.1	1.2	about 75

[a]EPA analysis of data from Yankel et al. (1977).

TABLE 11-23. GEOMETRIC MEAN BLOOD LEAD LEVELS BY AGE AND AREA FOR SUBJECTS LIVING NEAR THE IDAHO SMELTER

Area	Age Group 1	2	3	4	5	6	7	8	9	Teenage	Adult
1	69*	72	75	75	68	66	63	60	57	39	37
2	50	51	55	46	49	50	47	42	40	33	33
3	33	36	36	35	35	35	31	32	32	28	30
4	31	35	34	31	31	35	30	32	30		34
5	27	35	29	29	29	28	25	27	24		32
6	21	25	22	23	20	22	20	22	17		
7	28	30	28	32	30	26	37	30	20	35	32

*error in original publication (Yankel et al., 1977).

TABLE 11-24. AGE SPECIFIC REGRESSION COEFFICIENTS FOR THE ANALYSIS OF LOG-BLOOD-LEAD LEVELS IN THE IDAHO SMELTER STUDY

Age	Air	Dust	Occupation	Pica	Sex	Soil ($\times 10^4$)	Intercept	N
1	0.0467*	0.119†	0.0323	0.098	0.055	3.5	3.017	98
2	0.0405*	0.106†	0.0095	0.225*	0.002	20.6†	3.567	94
3	0.0472*	0.108†	0.0252	0.077	0.000	24.2*	3.220	115
4	0.0366*	0.107†	0.0348	0.117	0.032	32.1*	3.176	104
5	0.0388*	0.052	0.0363†	0.048	-0.081	23.4*	3.270	130
6	0.0361*	0.070	0.0369†	0.039	-0.092	38.4*	3.240	120
7	0.0413*	0.053	0.0240	0.106	-0.061	21.3†	3.329	113
8	0.0407*	0.051	0.0422†	0.010	-0.106†	16.2	3.076	105
9	0.0402*	0.081†	0.0087	0.108	-0.158*	11.6	3.477	104

* $p < 0.01$

† $p < 0.05$

Pica (coded absent = 0, present = 1) had a significant effect at age 2 years, but was insignificant elsewhere; at age 2 years, an approximate 25 percent elevation in blood lead is predicted in a child with pica, compared with an otherwise equivalent child without pica.

Occupation was significant at ages 5, 6 and 8 years; at the other ages, however, the sign of the coefficient was always positive, consistent with a greater lead burden being introduced into the home by parents working in the smelter complex.

Finally, sex (coded male = 0; female = 1) had a significant negative coefficient for ages 8 and 9 years, indicating that boys would have lead levels 15 percent higher than girls at this age, on the average. This phenomenon is enhanced by similar, but nonsignificant, negative coefficients for ages 5 to 7 years.

Snee (1982c) also reanalyzed the Idaho smelter data using a log-linear model. He used dummy variables for age, work status of the father, educational level of the father, and household dust level (cleanliness). The resulting model had a multiple R^2 of 0.67 and a residual standard deviation of 0.250 (geometric standard deviation of 1.28). The model showed that 2-year-olds had the highest blood lead levels. The blood lead inhalation slope was essentially the same as that of Yankel et al. (1977) and Walter et al. (1980).

The above non-linear analyses of the Idaho smelter study are the only analyses which suggest that the blood lead to air lead slope increases with increasing air lead, a finding in counterdistinction to the findings of decreasing slopes seen at high air lead exposures in other studies. An alternative to this would be to attempt to fit a linear model as described in Appendix 11-B. Exposure coefficients were estimated for each of the factors shown in Table 11-25. The results for the different covariates are similar to those of Snee (1982c) and Walter et al. (1980).

TABLE 11-25. ESTIMATED COEFFICIENTS* AND STANDARD ERRORS FOR THE IDAHO SMELTER STUDY

Factor	Coefficient	Asymptotic Standard Error
Intercept (μg/dl)	13.19	1.90
Air lead (μg/m^3)	1.53	0.064
Soil lead (1000 μg/g)	1.10	0.14
Sex (male=1, female=0)	1.31	0.59
Pica (eaters=1, noneaters=0)	2.22	0.90
Education (graduate training=0)	-	
At least high school	3.45	1.44
No high school	4.37	1.51
Cleanliness of home (clean=0)	-	
Moderately clean	3.00	0.65
Dirty	6.04	1.06
Age (1 year olds=0)	-	
2 years olds	4.66	1.48
3 years olds	5.48	1.32
4 years olds	3.16	1.32
5 years olds	2.82	1.25
6 years olds	2.74	1.24
7 years olds	0.81	1.23
8 years olds	-0.19	1.28
9 years olds	-1.50	1.21
Work status (no exposure=0)	-	
Lead or zinc worker	3.69	0.61

Residual standard deviation = 0.2576 (geometric standard deviation = 1.29)

Multiple R^2 = 0.662

Number of observations = 860

*Calculations made by EPA

Because the previous analyses noted above indicated a nonlinear relationship, a similar model with a quadratic air lead term added was also fitted. The coefficients for the other factors remained about the same, and the improvement in the model was marginally significant ($p = 0.05$). This model gave a slope of 1.16 at an air lead of 1 μg/m^3, and 1.39 at an air lead of 2 μg/m^3. Both the linear and quadratic models, along with Snee's (1982) model are shown in Figure 11-14. The points represent mean blood lead levels adjusted for the factors in Table 11-25 (except air lead) for each of the different exposure subpopulations.

Yankel et al. (1977), Walter et al. (1980) and Snee (1982c) make reference to a follow-up study conducted in 1975. The second study was undertaken to determine the effectiveness of control and remedial measures instituted after the 1974 study. Between August 1974 and August 1975, the mean annual air lead levels decreased at all stations monitored. In order of increasing distance from the smelter, the annual mean air lead levels for the one year preceding each drawing were 18.0 to 10.3 $\mu g/m^3$, 14.0 to 8.5 $\mu g/m^3$, 6.7 to 4.9 $\mu g/m^3$ and, finally 3.1 to 2.5 $\mu g/m^3$ at 10 to 24 km. Similar reductions were noted in house dust lead concentrations. In a separate report, von Lindern and Yankel (1976) described reductions in blood lead levels of children for whom determinations were made in both years. The results demonstrated that significant decreases in blood lead concentration resulted from exposure reductions.

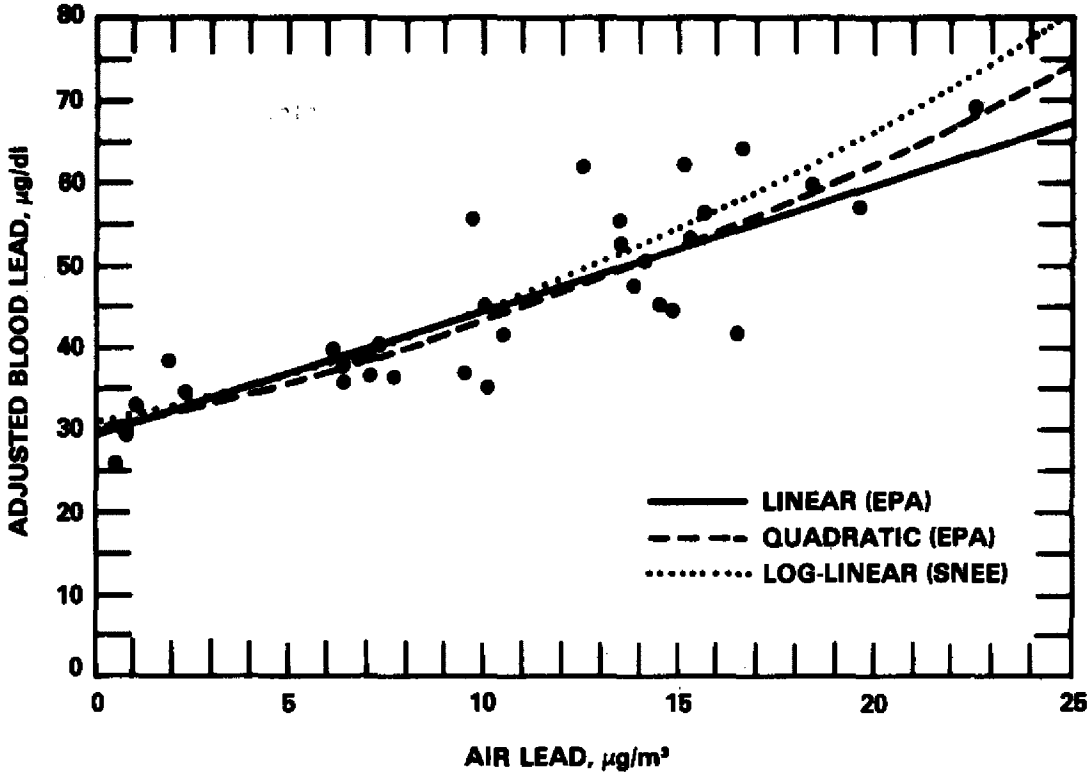

Figure 11-14. Fitted equations to Kellogg Idaho/Silver Valley adjusted blood lead data.

11.4.1.7 Omaha, Nebraska Studies. Exposure from both a primary and secondary smelter in the inner city area of Omaha, Nebraska, has been reported in a series of publications (Angle et al., 1974; Angle and McIntire, 1977; McIntire and Angle, 1973). During 1970 to 1977 children were studied from: an urban school at a site immediately adjacent to a small battery plant and downwind from two other lead emission sources; from schools in a mixed commercial-residential area; and from schools in a suburban setting. Children's blood lead levels were obtained by macro technique for 1970 and 1971, but Delves micro assay was used for 1972 and later. The differences for the change in techniques were taken into account in the presentation of the data. Air lead values were obtained by Hi-Vol samplers and dustfall values were also monitored. Table 11-26 presents the authors' summary of the entire data set, showing that as air lead values decrease and then increase, dustfall and blood lead values follow. The authors used regression models, both log-linear and semilog, to calculate (air lead)/(blood lead).

Specific reports present various aspects of the work. Black children in the two elementary schools closest to the battery plant had higher blood leads (34.1 μg/dl) than those in elementary and junior high schools farther away (26.3 μg/dl). Best estimates of the air exposures were 1.65 and 1.48 $\mu g/m^3$, respectively (McIntire and Angle, 1973). The latter study compared three populations: urban vs. suburban high school students, ages 14 and 18; urban black children, ages 10 to 12, vs. suburban whites, age 10 to 12; and blacks ages 10 to 12 with blood lead levels over 20 μg/dl vs. schoolmates with blood lead levels below 20 μg/dl (Angle et al., 1974). The urban vs. suburban high school children did not differ significantly, 22.3 ± 1.2 and 20.2 ± 7.0 μg/dl, respectively, with mean values of air lead concentrations of 0.43 and 0.29 $\mu g/m^3$. For 15 students who had environmental samples taken from their homes, correlation coefficients between blood lead levels and soil and housedust lead levels were 0.31 and 0.29, respectively.

Suburban 10-to-12-year-olds had lower blood lead levels than their urban counterparts, 17.1 ± 0.7 versus 21.7 ± 0.5 μg/dl (Angle et al., 1974). Air lead exposures were higher in the urban than in the suburban population, although the average exposure remained less than 1 $\mu g/m^3$. Dustfall lead measurements, however, were very much higher; 32.96 mg/m^2/month for urban 10-to-12-year-olds vs. 3.02 mg/m^2/month for suburban children.

Soil lead and house dust lead exposure levels were significantly higher for the urban black high lead group than for the urban low lead group. A significant correlation ($r = 0.49$) between blood lead and soil lead levels was found.

Angle has reanalyzed the Omaha study using all of the data on children. There were 1075 samples from which blood lead (μg/dl), air ($\mu g/m^3$), soil (μg/g) and house dust (μg/g) lead were available. The linear regression model, fitted in logarithmic form, was

$$\text{Pb-Blood} = 15.67 + 1.92\ \text{Pb-Air} + 0.00680\ \text{Pb-Soil} + 0.00718\ \text{Pb-House Dust}$$
$$(\pm 0.40) \quad (\pm 0.60) \quad (\pm 0.00097) \quad (\pm 0.00090)$$
$$(N = 1075,\ R^2 = 0.20,\ S^2 = 0.0901,\ GSD = 1.35)$$

Similar models fitted by age category produced much more variable results, possibly due to small ranges of variation in air lead within certain age categories.

TABLE 11-26. AIR, DUSTFALL AND BLOOD LEAD CONCENTRATIONS IN OMAHA, NE STUDY, 1970-1977[a]

Group	Air $\mu g/m^3$ (N)[b]	Dustfall, $\mu g/m^3$ - mo (N)[c]	Blood, µg/dl (N)[d]
All urban children, mixed commercial and residential site			
1970-71	1.48 ± 0.14(7;65)	--	31.4 ± 0.7(168)
1972-73	0.43 ± 0.08(8;72)	10.6 ± 0.3(6)	23.3 ± 0.3(211)
1974-75	0.10 ± 0.03(10;72)	6.0 ± 0.1(4)	20.4 ± 0.1(284)
1976-77	0.52 ± 0.07(12;47)	8.8 (7)	22.8 ± 0.7(38)
Children at school in a commercial site			
1970-71	1.69 ± 0.11(7;67)	--	34.6 ± 1.5(21)
1972-73	0.63 ± 0.15(8;74)	25.9 ± 0.6(5)	21.9 ± 0.6(54)
1974-75	0.10 ± 0.03(10;70)	14.3 ± 4.1(4)	19.2 ± 0.9(17)
1976-77	0.60 ± 0.10(12;42)	33.9 (7)	22.8 ± 0.7(38)
All suburban children in a residential site			
1970-71	0.79 ± 0.06(7;65)	--	--
1972-73	0.29 ± 0.04(8;73)	4.6 ± 1.1(6)	19.6 ± 0.5(81)
1974-75	0.12 ± 0.05(10;73)	2.9 ± 0.9(4)	14.4 ± 0.6(31)
1976-77	--	--	18.2 ± 0.3(185)

[a]Blood lead 1970-71 is by the macro technique, corrected for an established laboratory bias of 3 µg/dl, macro-micro; all other values are by Delves micro assay.

[b]N = Number of months; number of 24-hour samples.

[c]N = Number of months.

[d]N = Number of blood samples.

Source: Adapted from Angle and McIntire, 1977.

11.4.1.8 Roels et al. Studies. Roels et al. (1976, 1978, 1980) have conducted a series of studies in the vicinity of a lead smelter in Belgium. Roels et al. (1980) reports a follow-up study (1975) that included study populations from a rural-nonindustrialized area as well as from the lead smelter area. The rural group consisted of 45 children (11-14 years). The smelter area group consisted of 69 school children from three schools. These children were divided into two groups; group A (aged 10-13) lived less than 1 km from the smelter and their schools were very close to the smelter; group B consisted of school children living more than 1.5 km from the smelter and attending a school more distant from the smelter.

In 1974 the smelter emitted 270 kg of lead and the air lead levels were 1 to 2 orders of magnitude greater than the current Belgian background concentration for air lead (0.23 $\mu g/m^3$). Soil and vegetation were also contaminated with lead; within 1 km the soil lead level was 12,250 µg/g. The concentration of lead in drinking water was less than 5 µg/l.

Environmental assessment included air, soil and dust. Air monitoring for lead had been continuous since September 1973 at two sites, one for each of the two groups. In the rural area, air monitoring was done at two sites for five days using membrane pumps. Lead was analyzed by flameless atomic absorption spectrophotometry. Dust and soil samples were collected at the various school playgrounds. The soil sample was analyzed by flameless atomic absorption.

A 25 ml blood sample was collected from each child and immediately divided among three tubes. One tube was analyzed for lead content by flameless atomic absorption with background correction. Another tube was analyzed for ALA-D activity while the third was analyzed for FEP. FEP was determined by the Roels modification of the method of Sassa. ALA-D was assayed by the European standard method.

Air lead levels decreased from area A to area B. At both sites the airborne lead levels declined over the two years of monitoring. The amount of lead produced at this smelter during this time remained constant, about 100,000 tons/year. The median air lead level at the closer site (A) dropped from 3.2 to 1.2 $\mu g/m^3$, while at the far site (B) the median went from 1.6 to 0.5-0.8 $\mu g/m^3$. The rural area exposure levels did not vary over the study period, remaining rather constant at about 0.30 $\mu g/m^3$.

Both smelter vicinity groups showed signs of increased lead absorption relative to the rural population. Blood lead levels for group A were about three times those for the rural population (26 µg/dl vs. 9 µg/dl). The former blood lead levels were associated with about a 50 percent decrease in ALA-D activity and a 100 percent increase in FEP concentration. However, FEP levels were not different for group B and rural area residents.

Later surveys of children (Roels et al., 1980) were conducted in 1976, 1977 and 1978; the former two in autumn, the latter in spring. In total there were five surveys conducted yearly from 1974 to 1978. A group of age-matched controls from a rural area was studied each time except 1977. In 1976 and 1978 an urban group of children was also studied.

The overall age for the different groups ranged from 9 to 14 years (mean 11-12). The length of residence varied from 0.5 to 14 years (mean 7-10 years). The subjects were always recruited from the same five schools: one in the urban area, one in the rural area and three in the smelter area (two <1 km and one, 2.5 km away). Air lead levels decreased from 1977 to 1978. However, the soil lead levels in the vicinity of the smelter were still elevated (<1 km, soil lead 2000-6000 μg/g). Dustfall lead in the area of the near schools averaged 16.4-22.0 $mg/m^2 \cdot day$ at 500 m from the stack, 5.8-7.2 $mg/m^2 \cdot day$ at 700 m, about 2 $mg/m^2 \cdot day$ at 1000 m and fluctuating around 0.5-1 $mg/m^2 \cdot day$ at 1.5 km and beyond. The particle size was predominantly 2 μm in diameter with a secondary peak between 4 and 9 μm. The particle size declined with increasing distance from the smelter (0.7-2.4 km).

In all, 661 children (328 boys and 333 girls) were studied over the years. Two hundred fourteen children came from less than 1 km from the smelter, 169 children from 1.5 to 2.5 km from the plant, 55 children lived in the urban area and 223 children lived in the rural area.

The air lead and blood lead results for the five years are presented as Table 11-27. The reported air leads are not calendar year averages. The table shows that blood lead levels (electrothermal atomic absorption spectrophotometry) are lower in the girls than the boys. Within 1 km of the smelter no consistent improvement in air lead levels was noted over the years of the study. The mean blood leads for the children living at about 2.5 km from the smelter never exceeded 20 μg/dl since 1975, although they were higher than for urban and rural children.

The researchers then investigated the importance of the various sources of lead in determining blood lead levels. Data were available from the 1976 survey on air, dust and hand lead levels. Boys had higher hand dust lead than girls. Unfortunately, the regression analyses performed on these data were based on the group means of four groups.

EPA has reanalyzed the 1976 study using original data provided by Dr. Roels on the 148 children. The air lead, playground dust lead, and hand lead concentrations were all highly correlated with each other. The hand lead measurements are used here with due regard for their limitations, because day-to-day variations in hand lead for individual children are believed to be very large. However, even though repeated measurements were not available, this is among the most usable quantitative evidence on the role of ingested hand dust in childhood lead absorption.

Total lead content per hand is probably more directly related to ingested lead than is the lead concentration in the hand dust. The linear regression model used above was fitted by EPA using lead in air ($\mu g/m^3$), lead in hand dust (μg/hand), lead in playground dust (μg/g) and sex as covariates of blood lead. The lead variables were highly correlated, resulting in a

TABLE 11-27. MEAN AIRBORNE AND BLOOD LEAD LEVELS RECORDED DURING FIVE DISTINCT SURVEYS (1974 to 1978) FOR STUDY POPULATIONS OF 11-YEAR-OLD CHILDREN LIVING LESS THAN 1 km OR 2.5 km FROM A LEAD SMELTER, OR LIVING IN A RURAL OR URBAN AREA

Study populations	Pb-Air ($\mu g/m^3$)		Blood lead concentration ($\mu g/dl$) Total Population n	Mean ± SD	Boys n	Mean ± SD	Girls n	Mean ± SD
1 Survey (1974)	<1 km	4.06	37	30.1 ± 5.7	14	31.0 ± 5.5	23	29.6 ± 5.9
	2.5 km	1.00	--	--	14	21.1 ± 3.4	--	--
	Rural	0.29	92	9.4 ± 2.1	28	9.7 ± 1.6	64	9.3 ± 2.2
2 Survey (1975)	<1 km	2.94	40	26.4 ± 7.3	19	27.4 ± 6.5	21	25.4 ± 8.1
	2.5 km	0.74	29	13.6 ± 3.3	17	14.8 ± 3.6	12	11.9 ± 1.9
	Rural	0.31	45	9.1 ± 3.1	14	8.2 ± 2.1	31	9.5 ± 3.4
3 Survey (1976)	<1 km	3.67	38	24.6 ± 8.7	18	28.7 ± 8.0	20	20.8 ± 7.6
	2.5 km	0.80	40	13.3 ± 4.4	24	15.6 ± 2.9	16	9.8 ± 3.8
	Urban	0.45	26	10.4 ± 2.0	17	10.6 ± 2.0	9	9.9 ± 2.0
	Rural	0.30	44	9.0 ± 2.0	21	9.2 ± 2.3	23	8.7 ± 1.7
4 Survey (1977)	<1 km	3.42	56	28.9 ± 6.5	27	31.7 ± 9.5	29	26.4 ± 8.7
	2.5 km	0.49	50	14.8 ± 4.7	34	15.7 ± 4.8	16	13.0 ± 4.3
5 Survey (1978)	1 km	2.68	43	27.8 ± 9.3	20	29.3 ± 9.8	23	26.5 ± 8.9
	2.5 km	0.54	36	16.0 ± 3.8	26	16.6 ± 3.5	10	14.3 ± 4.2
	Urban	0.56	29	12.7 ± 3.1	18	13.4 ± 2.3	11	11.5 ± 4.0
	Rural	0.37	42	10.7 ± 2.8	17	11.9 ± 3.0	25	10.0 ± 2.4

Source: Roels et al. 1980.

statistically significant regression but not statistically significant coefficients. Thus the playground dust measurement was dropped and the following model obtained with almost as small a residual sum of squares,

$$\ln(\text{Pb-Blood}) = \underset{(\pm.45)}{\ln(7.37} + \underset{(\pm.58)}{2.46}\ \text{Pb-Air} + \underset{(\pm.0062)}{0.0195}\ \text{Pb-Hand} + \underset{(\pm0.56)}{2.10}\ \text{Male})$$

The fitted model for the 148 observations gave an R^2 of 0.654 and a mean square error (S^2) of 0.0836 (GSD = 1.335). The significance of the estimated coefficient establishes that intake of lead-bearing dust from the hands of children does play a role in childhood lead absorption over and above the role that can be assigned to inhalation of air lead. Individual habits of mouthing probably also affect lead absorption along this pathway. Note too that the estimated inhalation slope, 2.46, is somewhat larger than most estimates for adults. However, the effect of ingestion of hand dust appears to be almost as large as the effect of air lead inhalation in children of this age (9-14 years). Roels et al. (1980), using group means,

concluded that the quantitative contribution of hand lead to children's blood lead levels was far greater than that of air lead.

The high mutual correlations among air, hand, and dust lead suggest the use of their principal components or principal factors as predictors. Only the first principal component (which accounted for 91% of the total variance in lead exposure) proved a statistically significant covariate of blood lead. In this form the model could be expressed as

$$\ln(\text{Pb-Blood}) = \ln(7.42 + 1.56\text{Pb-Air} + 0.0120\text{Pb-Hand} + 0.00212\text{Pb-Dust} + 2.29\ \text{Male})$$

The estimated standard error on the inhalation slope is ±0.47. The difference between these inhalation slope and hand lead coefficients is an example of the partial attribution of the effects of measured lead exposure sources to those sources that are not measured.

11.4.1.9 Other Studies Relating Blood Lead Levels to Air Exposure. The following studies also provide information on the relationship of blood lead to air lead exposures, although they are less useful in accurately estimating the slope at lower exposure levels. The first group of studies are population studies with less accurate estimates of individual exposures. The second group of studies represent industrial exposures at very high air lead levels in which the response of blood lead appears to be substantially different than at ambient air levels.

The Tepper and Levin (1975) study included both air and blood lead measurements. Housewives were recruited from locations in the vicinity of air monitors. Table 11-28 presents the geometric mean air lead and adjusted geometric mean blood lead values for this study. These values were calculated by Hasselblad and Nelson (1975). Geometric mean air lead values ranged from 0.17 to 3.39 $\mu g/m^3$, and geometric mean blood lead values ranged from 12.7 to 20.1 µg/dl.

Nordman (1975) reported a population study from Finland in which data from five urban and two rural areas were compared. Air lead data were collected by stationary samplers. All levels were comparatively low, particularly in the rural environment, where a concentration of 0.025 $\mu g/m^3$ was seen. Urban-suburban levels ranged from 0.43 to 1.32 $\mu g/m^3$.

A study was undertaken by Tsuchiya et al. (1975) in Tokyo using male policemen who worked, but not necessarily lived, in the vicinity of air samplers. In this study, five zones were established, based on degree of urbanization, ranging from central city to suburban. Air monitors were established at various police stations within each zone. Air sampling was conducted from September 1971 to September 1972; blood and urine samples were obtained from 2283 policemen in August and September 1971. Findings are presented in Table 11-29.

Goldsmith (1974) obtained data for elementary school (9- and 10-year-olds) and high school students in 10 California communities. Lowest air lead exposures were 0.28 $\mu g/m^3$ and highest were 3.4 $\mu g/m^3$. For boys in elementary school, blood lead levels ranged from 14.3 to

TABLE 11-28. GEOMETRIC MEAN AIR LEAD AND ADJUSTED BLOOD LEAD LEVELS FOR 11 COMMUNITIES IN STUDY OF TEPPER AND LEVIN (1975) AS REPORTED BY HASSELBLAD AND NELSON (1975)

Community	Geometric mean air lead, $\mu g/m^3$	Age and smoking adjusted geometric mean blood lead, $\mu g/dl$	Sample size
Los Alamos, NM	0.17	15.1	185
Okeana, OH	0.32	16.1	156
Houston, TX	0.85	12.7	186
Port Washington, NY	1.13	15.3	196
Ardmore, PA	1.15	17.9	148
Lombard, IL	1.18	14.0	204
Washington, DC	1.19	18.7	219
Philadelphia, PA	1.67	20.1	136
Bridgeport, IL	1.76	17.6	146
Greenwich Village, NY	2.08	16.5	139
Pasadena, CA	3.39	17.6	194

Multiple $R^2 = 0.240$

Residual standard deviation = 0.262 (geometric standard deviation = 1.30)

TABLE 11-29. MEAN AIR AND BLOOD LEAD VALUES FOR FIVE ZONES IN TOKYO STUDY

Zones	Air lead, $\mu g/m^3$	Blood lead, $\mu g/100$ g
1	0.024	17.0
2	0.198	17.1
3	0.444	16.8
4	0.831	18.0
5	1.157	19.7

Source: Tsuchiya et al. 1975.

23.3 µg/dl; those for girls ranged from 13.8 to 20.4 µg/dl for the same range of air lead exposures. The high school student population was made up of only males from some of the 10 towns. The air lead range was 0.77 to 2.75 µg/m^3, and the blood lead range was 9.0 to 12.1 µg/dl. The high school students with the highest blood lead levels did not come from the town with the highest air lead value. However, a considerable lag time occurred between the collection and analysis of the blood samples. In one of the communities the blood samples were refrigerated rather than frozen.

Another California study (Johnson et al., 1975, 1976) examined blood lead levels in relation to exposure to automotive lead in two communities, Los Angeles and Lancaster (a city in the high desert). Los Angeles residents studied were individuals living in the vicinity of heavily traveled freeways within the city. They included groups of males and females, aged 1 through 16, 17 through 34, and 34 and over. The persons selected from Lancaster represented similar age and sex distributions. On two consecutive days, blood, urine and fecal samples were collected. Air samples were collected from one Hi-Vol sampler in Los Angeles, located near a freeway, and two such samplers in Lancaster. The Los Angeles sampler collected for 7 days; the two in Lancaster operated for 14 days. Soil samples were collected in each area in the vicinity of study subjects.

Lead in ambient air along the Los Angeles freeway averaged 6.3 ± 0.7 µg/m^3 and, in the Lancaster area, the average was 0.6 ± 0.2 µg/m^3. The mean soil lead in Los Angeles was 3633 µg/g, whereas that found in Lancaster was 66.9 µg/g. Higher blood lead concentrations were found in Los Angeles residents than in individuals living in the control area for all age groups studied. Differences between Los Angeles and Lancaster groups were significant with the sole exception of the older males. Snee (1981) has pointed out a disparity between blood samples taken on consecutive days from the same child in the study. This calls into question the validity of using this study to quantify the air lead to blood lead relationship.

Daines et al. (1972) studied black women living near a heavily traveled highway in New Jersey. The subjects lived in houses on streets paralleling the highway at three distances: 3.7, 38.1 and 121.9 m. Air lead as well as blood lead levels were measured. Mean annual air lead concentrations were 4.60, 2.41 and 2.24 µg/m^3, respectively, for the three distances. The mean air lead concentration for the area closest to the highway was significantly different from that in both the second and third, but the mean air lead concentration of the third area was not significantly different from that of the second. The results of the blood lead determinations paralleled those of the air lead. Mean blood lead levels of the three groups of women, in order of increasing distance, were 23.1, 17.4 and 17.6 µg/dl, respectively. Again, the first group showed a significantly higher mean than the other two, but the second and third groups' blood lead levels were similar to each other. Daines et al. (1972), in the same publication, reported a second study in which the distances from the highway were 33.5 and 457 meters and in which the subjects were white upper middle class women. The air

lead levels were trivially different at these two distances, and the blood lead levels did not differ either. Because the residents nearest the road were already 33 m from the highway, the differences in air lead may have been insufficient to be reflected in the blood lead levels. (See Chapter 7)

A summary of linear relationships for other population studies has been extracted from Snee (1981) and is shown in Table 11-30. The Fugas study is described later in Section 11.5.2.3. There is a large range of slope values (-0.1 to 3.1) with most studies in the range of 1.0 to 2.0. Additional information on the more directly relevant studies is given in the Summary Section 11.4.1.10.

TABLE 11-30. BLOOD LEAD-AIR LEAD SLOPES FOR SEVERAL POPULATION STUDIES AS CALCULATED BY SNEE

Study	No. Subjects	Sex	Slope	95% confidence Intervals
Tepper & Levin (1975)	1935	Female	1.1	±1.8
Johnson et al. (1975)	65	Male	0.8	±0.7
	96	Female	0.8	±0.6
Nordman (1975)	536	Male	1.2	±1.0
	478	Female	0.6	±0.9
Tsuchiya et al.(1975)	537	Male	3.1	±2.2
Goldsmith (1974)	89	Male	-0.1	±0.7
	79	Female	0.7	±0.7
Fugas (1977)	352	Male	2.2	±0.7
Daines et al. (1972)	61	Female (spring)	1.6	±1.7
	88	Female (fall)	2.4	±1.2
Johnson et al. (1975)	37[a]	Male (children)	1.4	±0.6
	43	Female (children)	1.1	±0.6
Goldsmith (1974)	486	Male & Female (children)	2.0	±1.3

[a]Outlier results for four subjects deleted.
Source: Snee, 1981.

There is a great deal of information on blood lead responses to air lead exposures of workers in lead-related occupations. Almost all such exposures are at air lead levels far in excess of typical non-occupational exposures. The blood lead vs. air lead slope β is very much smaller at high blood and air levels. Analyses of certain studies are shown in Table 11-31.

TABLE 11-32. CROSS-SECTIONAL OBSERVATIONAL STUDY WITH MEASURED INDIVIDUAL AIR LEAD EXPOSURE

Study	Analysis	Model	R^2	Model d.f.	Slope at an air lead of 1.0 $\mu g/m^3$	Slope at an air lead of 2.0 $\mu g/m^3$
Azar et al. (1975) Study done in 1970-1971 in five U.S. cities, total sample size = 149. Blood leads ranged from 8 to 40 µg/dl. Air leads ranged from 0.2 to 9.1 $\mu g/m^3$	Azar et al. (1975)	ln (PBB) = 0.153 ln (PBA) + separate intercepts for each group	0.502	6	2.57 (1.23, 3.91)	1.43 (0.64, 2.30)
	Snee (1982b)	ln (PBB) = 0.2669 ln (PBA + separate background for each group) + 1.0842	0.497	7	1.12 (0.29, 1.94)	0.96 (0.25, 1.66)
	Hammond et al. (1981)	$(PBB)^{-1.019} = 0.179\ (PBA + \text{separate background for each group})^{0.104} - 0.098$	0.49	8	1.08	1.07
	EPA	ln(PBB) = ln(1.318 PBA + separate background for each group)	0.491	6	1.32 (0.46, 2.17)	1.32 (0.46, 2.17)
	EPA	$\ln(PBB) = \ln(2.902\ PBA - 0.257\ PBA^2 + \text{separate background for each group})$	0.504	7	2.39	1.87
	EPA	ln(PBB) = ln(1.342 PBA + separate background + age slope x age)	0.499	7	1.34 (0.32, 2.37)	1.34 (0.32, 2.37)
	EPA	ln(PBB) = ln(1.593 PBA = common intercept + age x separate age slope)	0.489	7	1.59 (0.76, 2.42)	1.59 (0.76, 2.42)
	EPA	ln(PBB) = ln(1.255 PBA + separate background + age + separate age slope)	0.521	11	1.26 (0.46, 2.05)	1.26 (0.46, 2.05)
	EPA	ln(PBB) = 0.25 ln-(PBA + separate background + age x separate age slope)	0.514	12	about 1.0 (varies by city)	about 1.0 (varies by city)

Note: PBB stands for blood lead (µg/dl); PBA stands for air lead ($\mu g/m^3$); slope means rate of change of blood lead per unit change in air lead at the stated air lead value. The 95 percent confidence intervals for the slope are given in parentheses. These are approximate and should be used with caution. The analyses labelled "EPA" are calculated from the original authors' data.

TABLE 11-32. CROSS-SECTIONAL OBSERVATIONAL STUDY WITH MEASURED INDIVIDUAL AIR LEAD EXPOSURE

Study	Analysis	Model	R^2	Model d.f.	Slope at an air lead of 1.0 $\mu g/m^3$	Slope at an air lead of 2.0 $\mu g/m^3$
Azar et al. (1975) Study done in 1970-1971 in five U.S. cities, total sample size = 149. Blood leads ranged from 8 to 40 µg/dl. Air leads ranged from 0.2 to 9.1 $\mu g/m^3$	Azar et al. (1975)	ln (PBB) = 0.153 ln (PBA) + separate intercepts for each group	0.502	6	2.57 (1.23, 3.91)	1.43 (0.64, 2.30)
	Snee (1982b)	ln (PBB) = 0.2669 ln (PBA + separate background for each group) + 1.0842	0.497	7	1.12 (0.29, 1.94)	0.96 (0.25, 1.66)
	Hammond et al. (1981)	$(PBB)^{-1.019} = 0.179\ (PBA + \text{separate background for each group})^{0.104} - 0.098$	0.49	8	1.08	1.07
	EPA	ln(PBB) = ln(1.318 PBA + separate background for each group)	0.491	6	1.32 (0.46, 2.17)	1.32 (0.46, 2.17)
	EPA	ln(PBB) = ln(2.902 PBA - 0.257 PBA^2 + separate background for each group)	0.504	7	2.39	1.87
	EPA	ln(PBB) = ln(1.342 PBA + separate background + age slope x age)	0.499	7	1.34 (0.32, 2.37)	1.34 (0.32, 2.37)
	EPA	ln(PBB) = ln(1.593 PBA = common intercept + age x separate age slope)	0.489	7	1.59 (0.76, 2.42)	1.59 (0.76, 2.42)
	EPA	ln(PBB) = ln(1.255 PBA + separate background + age + separate age slope)	0.521	11	1.26 (0.46, 2.05)	1.26 (0.46, 2.05)
	EPA	ln(PBB) = 0.25 ln-(PBA + separate background + age x separate age slope)	0.514	12	about 1.0 (varies by city)	about 1.0 (varies by city)

Note: PBB stands for blood lead (µg/dl); PBA stands for air lead ($\mu g/m^3$); slope means rate of change of blood lead per unit change in air lead at the stated air lead value. The 95 percent confidence intervals for the slope are given in parentheses. These are approximate and should be used with caution. The analyses labelled "EPA" are calculated from the original authors' data.

TABLE 11-33. CROSS-SECTIONAL OBSERVATIONAL STUDIES ON CHILDREN WITH ESTIMATED AIR EXPOSURES

Study	Analysis	Model	R^2	Model d.f.	Slope at an air lead of 1.0 µg/m³	Slope at an air lead of 5.0 µg/m³
Kellogg Idaho/Silver Valley study conducted in 1974 based on about 880 children. Air leads ranged from 0.5 to 22 µg/m³. Blood leads ranged from 11 to 164	Yankel et al. (1977)	$\ln(PBB) = 0.041\ PBA + 2.1x10^{-5}$ soil + 0.087 dust − 0.018 age + 0.024 occupation + 3.14	0.622	6	1.16 (1.09, 1.23)	1.37 (1.27, 1.46)
	Snee (1982c)	$\ln(PBB) = 0.039\ PBA + 0.065 \ln$ (soil) + terms for sex, occupation, cleanliness, education, pica	0.666	25	1.13 (1.06, 1.20)	1.32 (1.23, 1.42)
	EPA	$\ln(PBB) = \ln(1.52\ PBA$ to 0.0011 soil + terms for sex, occupation, cleanliness, education, pica)	0.655	18	1.52	1.52
	EPA	$\ln(PBB) = \ln(1.13\ PBA + 0.026\ PBA^2$ + terms for soil, sex, occupation, cleanliness, education, pica)	0.656	19	1.16	1.39
	Walter et al. (1980)	$\ln(PBB) =$ separate slopes for air, dust, occupation, pica sex and soil by age	0.56 to 0.70	7	1.01 to 1.26	1.18 to 1.48
Kellogg Idaho/Silver Valley study as above restricted to 537 children with air leads below 10 µg/m³	Snee (1982a)	$\ln(PBB) = 0.039\ PBA + 0.055 \ln$ (soil) + terms for sex, occupation cleanliness, education, pica	0.347	25	1.07 (0.89, 1.25)	1.25 (1.01, 1.50)
Roels et al. (1980)	Roels et al. (1980) based on 8 groups	$PBB = 0.007\ PBA + 11.50 \log(PB\text{-}Hand) - 4.27$	0.65	3	0.007	0.007
	EPA analysis on 148 subjects	$\ln(PBB) = \ln(2.46\ PBA + 0.0195$ (Pb-Hand) + 2.1 (Male) + 7.37)	0.654	4	2.46 (1.31,3.61)	2.46 (1.31,3.61)
Angle and McIntire (1979)	Angle and McIntire (1979) on 832 samples ages 6-18	$\ln(PBB) = \ln(8.1) + 0.03 \ln$ (PBA) + 0.10 ln (PB-Soil) + 0.07 ln (Pb-House Dust)	0.21	4	0.6	0.14
	Angle et al. (1983) on 1074 samples for ages 1-18	$\ln(PBB) = \ln(1.92\ PBA + 0.00680$ Pb-Soil + 0.00718 Pb-House Dust + 15.67)	0.199	4	1.92 (0.74,3.10)	1.92 (0.74,3.10)
	832 samples ages 6 to 18	$\ln(PBB) = \ln(4.40\ PBA$ to .00457 Pb-Soil + 0.00336 Pb-House Dust + 16.21)	0.262	4	4.40 (3.20,5.60)	4.40 (3.20,5.60)

Note: PBB stands for blood lead (µg/dl); PBA stands for air lead (µg/m³); slope means rate of change of blood lead per unit change in air lead at the stated air lead value. The 95 percent confidence intervals for the slope are given in parentheses. These are approximate and should be used with caution. The analyses labelled "EPA" are calculated from the original authors' data.

TABLE 11-34. LONGITUDINAL EXPERIMENTAL STUDIES WITH MEASURED INDIVIDUAL AIR LEAD EXPOSURE

Experiment	Analysis	Model	Air Lead $\mu g/m^3$	Blood Lead $\mu g/dl$
Kehoe 1950-1971	Gross (1981)	Δ PBB = 0.57 Δ PBA	0.6 to 36	18 to 41
1960-1969	Hammond et al.(1981)	Δ PBB = $\beta_i \Delta$ PBA, β_i by subject from -0.6 to 2.94	"	"
	Snee (1981)	Δ PBB = $\beta_i \Delta$ PBA, β_i by subject from 0.4 to 2.4	"	"
	EPA	PBB = β_i PBA + background, β_i by subject from -.34 to 2.60	0.6 to 9	18 to 29
Griffin et al.	Knelson et al.(1973)	Δ PBB = 0.327 PBA + 3.236 + (2.10 PBA + 1.96) (ln PBA + β_i) by subject	0.15, 3.2	11 to 32
1971-1972	Hammond et al.(1981)	Δ PBB = $\beta \Delta$ PBA, β = 1.90 at 3.2 and β = 1.54 at 10.9	0.15, 10.9	14 to 43
	Snee (1981)	Δ PBB = $\beta_i \Delta$ PBA, β_i by subject, β = 2.3 at 3.2 and β = 1.5 at 10.9		
	EPA	Δ PBB = $\beta_i \Delta$ PBA, β_i by subject, mean β = 1.52 at 3.2 and β = 1.77 at 10.9		
Chamberlain et al. 1973-1978	Chamberlain et al. (1978)	Δ PBB = $\beta \Delta$PBA, β = 1.2 calculated		
	EPA	Δ PBB = $\beta \Delta$PBA, β = 2.7 calculated		
Rabinowitz et al. 1973-1974	Snee (1981)	Δ PBB = β_i ΔPBA, β_i by subject from 1.7 to 3.9	0.2 to 2	14 to 28
	EPA	Δ PBB = β_i ΔPBA, β_i by subject from 1.59 to 3.56		

The blood lead inhalation slope estimates vary appreciably from one subject to another in experimental and clinical studies, and from one study to another. The weighted slope and standard error estimates from the Griffin study in Table 11-16 (1.75 ± 0.35) were combined with those calculated similarly for the Rabinowitz study in Table 11-19 (2.14 ± 0.47) and the Kehoe study in Table 11-20 (1.25 ± 0.35 setting DH = 0), yielding a pooled weighted slope estimate of 1.64 ± 0.22 μg/dl per $\mu g/m^3$. There are some advantages in using these experimental studies on adult males, but certain deficiencies need to be acknowledged. The Kehoe study exposed subjects to a wide range of exposure levels while in the exposure chamber, but did not control air lead exposures outside the chamber. The Griffin study provided reasonable control of air lead exposure during the experiment, but difficulties in defining the non-inhalation baseline for blood lead (especially in the important experiment at 3.2 $\mu g/m^3$) add much uncertainty to the estimate. The Rabinowitz study controlled well for diet and other factors and since they used stable lead isotope tracers, they had no baseline problem. However, the actual air lead exposure of these subjects outside the metabolic ward was not well determined.

Among population studies, only the Azar study provides a slope estimate in which air lead exposures are known for individuals. However, there was no control of dietary lead intake or other factors that affect blood lead levels, and slope estimates assuming only air lead and location as covariables (1.32 ± 0.38) are not significantly different from the pooled experimental studies.

Snee and Pfeifer (1983) have extensively analyzed the observational studies, tested the equivalence of slope estimates using pooled within-study and between-study variance components, and estimated the common slope. The result of five population studies on adult males (Azar, Johnson, Nordman, Tsuchiya, Fugas) was an inhalation slope estimate ±95 percent confidence limits of 1.4 ± 0.6. For six populations of adult females [Tepper-Levin, Johnson, Nordman, Goldsmith, Daines (spring), Daines (fall)], the slope was 0.9 ± 0.4. For four populations of children [Johnson (male), Johnson (female), Yankel, Goldsmith], the slope estimate was 1.3 ± 0.4. The between-study variance component was not significant for any group so defined, and when these groups were pooled and combined with the Griffin subjects, the slope estimate for all subjects was 1.2 ± 0.2.

The Azar slope estimate was not combined with the experimental estimates because of the lack of control on non-inhalation exposures. Similarly, the other population studies in Table 11-30 were not pooled because of the uncertainty about both inhalation and non-inhalation lead exposures. These studies, as a group, have lower slope estimates than the individual experimental studies.

There are no experimental inhalation studies on adult females or on children. The inhalation slope for women should be roughly the same as that for men, assuming proportionally smaller air intake and blood volume. The assumption of proportional size is less plausible

for children. Slope estimates for children from population studies have been used in which some other important covariates of lead absorption were controlled or measured, e.g., age, sex, dust exposure in the environment or on the hands. Inhalation slopes were estimated for the studies of Angle and McIntire (1.92 ± 0.60), Roels (2.46 ± 0.58) and Yankel et al. (1.53 ± 0.064). The standard error of the Yankel study is extremely low and a weighted pooled slope estimate for children would reflect essentially that study alone. In this case the small standard error estimate is attributable to the very large range of air lead exposures of children in the Silver Valley (up to 22 $\mu g/m^3$). The relationship is in fact not linear, but increases more rapidly in the upper range of air lead exposures. The slope estimate at lower air lead concentrations may not wholly reflect uncertainty about the shape of the curve at higher concentrations. The unweighted mean slope of the three studies and its standard error estimate are 1.97 ± 0.39.

This estimate was not combined with the child population studies of Johnson or Goldsmith. The Johnson study slope estimate used air lead measured at only two sites and is sensitive to assumptions about data outliers (Snee, 1981), which adds a large non-statistical uncertainty to the slope estimate. The Goldsmith slope estimate for children (2.0 ± 0.65) is close to the estimate derived above, but was not used due to non-statistical uncertainties about blood lead collection and storage.

One can summarize the situation briefly:

(1) The experimental studies at lower air lead levels, 3.2 $\mu g/m^3$ or less, and lower blood levels, typically 30 µg/dl or less, have linear blood lead inhalation relationships with slopes β_i of 0 to 3.6 for most subjects. A typical value of 1.64 ± 0.22 may be assumed for adults.

(2) Population cross-sectional studies at lower air lead and blood lead levels are approximately linear with slopes β of 0.8 to 2.0.

(3) Cross-sectional studies in occupational exposures in which air lead levels are higher (much above 10 $\mu g/m^3$) and blood lead levels are higher (above 40 µg/dl), show a much more shallow linear blood lead inhalation relation. The slope β is in the range 0.03 to 0.2.

(4) Cross-sectional and experimental studies at levels of air lead somewhat above the higher ambient exposures (9 to 36 $\mu g/m^3$) and blood leads of 30 to 40 µg/dl can be described either by a nonlinear relationship with decreasing slope or by a linear relationship with intermediate slope, approximately $\beta = 0.5$. Several biological mechanisms for these differences have been discussed (Hammond et al., 1981; O'Flaherty et al., 1982; Chamberlain, 1983; Chamberlain and Heard, 1981). Since no explanation for the decrease in steepness of the blood lead inhalation response to higher air lead levels has been generally accepted at this time, there is little basis on which to select an interpolation formula from low air lead to high air lead exposures. The increased steepness of the inhalation curve for the Silver Valley/ Kellogg study is inconsistent with the

other studies presented. It may be that smelter situations are unique and must be analyzed differently, or it may be that the curvature is the result of imprecise exposure estimates.

(5) The blood-lead inhalation slope for children is at least as steep as that for adults, with an estimate of 1.97 ± 0.39 from three major studies (Yankel et al., 1977; Roels, et al. (1980); Angle and McIntire, 1979).

11.4.2 Dietary Lead Exposures Including Water

Another major pathway by which lead enters the body is by ingestion. As noted in Chapters 6 and 7, the recycling of both natural and anthropogenic lead in the environment results in a certain amount of lead being found in the food we eat and the water we drink. Both of these environmental media provide external exposures to lead that ultimately increase internal exposure levels in addition to internal lead elevations caused by direct inhalation of lead in air. The Nutrition Foundation Report (1982) presents a compilation of recent estimates of dietary intakes in the United States and Canada. The report gives information on relationships between external lead exposures and blood lead levels. The mechanisms and absorption rates for uptake of lead from food and water are described in Chapter 10. The purpose of the present section is to establish (analogously to Section 11.4.1) the relationships between external exposures to lead in food and drinking water and resulting internal lead exposures.

The establishment of these external and internal lead exposure relationships for the environmental media of food and water, however, is complicated by the inherent relationship between food and water. First, the largest component of food by weight is water. Second, drinking water is used for food preparation and, as shown in Section 7.3.1.3 provides additional quantities of lead that are appropriately included as part of external lead exposures ascribed to food. Third, the quantity of liquid consumed daily by people varies greatly and substitutions are made among different sources of liquid: soft drinks, coffee, tea, etc., and drinking water. Therefore, at best, any values of water lead intake used in drinking water calculations are somewhat problematic.

A further troubling fact is the influence of lead in the construction of plumbing facilities. Studies discussed in Section 7.3.2.1.3 have pointed out the substantial lead exposures in drinking water that can result from the use of lead pipes in the delivery of water to the tap. This problem is thought to occur only in limited geographic areas in the U.S. However, where the problem is present, substantial water lead exposures occur. In these areas one cannot make a simplifying assumption that the lead concentration in the water component of food is similar to that of drinking water. But rather one is adding a potentially major additional lead exposure to the equation.

Studies that have attempted to relate blood lead levels to ingested lead exposures have used three approaches to estimate the external lead exposures involved: duplicate meals, fecal lead determinations, and market basket surveys. In duplicate diet studies, estimated lead exposures are assessed by having subjects put aside a duplicate of what they eat at each meal for a limited period of time. These studies probably provide a good, but short term, estimate of the ingestion intake. However, the procedures available to analyze lead in foods have historically been subject to inaccuracies. Hence, the total validity of data from this approach has not been established. Studies relying on the use of fecal lead determinations face two major difficulties. First, this procedure involves the use of a mathematical estimate of the overall absorption coefficient from the gut to estimate the external exposure. Until recently, these estimates have not been well documented and were assumed to be relatively constant. Newer data discussed later show a much wider variability in the observed absorption coefficients than was thought to be true. These new observations cloud the utility of studies using this method to establish external/internal exposure relationships. Second, it is difficult to collect a representative sample.

The last approach is the market basket approach. This approach uses the observed lead concentrations for a variety of food items coupled with estimated dietary consumption of the particular food items. Some studies use national estimates of typical consumption patterns upon which to base the estimated exposures. Other studies actually record the daily dietary intakes. This approach faces similar analytic problems to those found in the duplicate diet pproach. It also faces the problem of getting accurate estimates of dietary intakes. The most current total diet study (Pennington, 1983) is described in Section 7.3.1.2.

Exposures to lead in the diet are thought to have decreased from the 1940's. Estimates om that period were in the range of 400-500 µg/day for U.S. populations. Current estimates or U.S. populations are under 100 µg/day for adults. Unfortunately, a good historical record regarding the time course of dietary exposures is not available. In the years 1978-82, efforts have been made by the American food canning industry in cooperation with the FDA to reduce the lead contamination of canned food. Data presented in Section 7.3.1.2.5 confirm the success of this effort.

The specific studies available for review regarding dietary exposures will be organized into three major divisions: lead ingestion from typical diets, lead ingestion from experimental dietary supplements and inadvertent lead ingestion from lead plumbing.

11.4.2.1 Lead Ingestion from Typical Diets.

11.4.2.1.1 Ryu study on infants and toddlers. Ryu et al. (1983) reported a study of four breast-fed infants and 25 formula-fed infants from 8 days to 196 days of age. After 112 days, the formula-fed infants were separated into a group of 10 who received carton milk and a

second group of seven who received either canned formula or heat-treated milk in cans. In addition to food concentrations, data were collected on air, dust and water lead. Hemoglobin and FEP were also measured.

The trends in blood lead for the formula-fed infants are shown in Table 11-35. The results up to day 112 are averaged for all 25 infants. The estimated average intake was 17 µg/day for this time period. After day 112, the subgroup of seven infants fed either canned formula or heat-treated cow's milk in cans (higher lead), had average estimated lead intake of 61 µg/day. This resulted in an increase of 7.2 µg/dl in the average blood lead for an increase of 45 µg/day in lead intake. The estimated slope from this data is 0.16.

TABLE 11-35. BLOOD LEAD LEVELS AND LEAD INTAKE VALUES FOR INFANTS IN THE STUDY OF RYU ET AL.

Age in Days	Blood lead of combined group (µg/dl)		Average lead intake of combined group (µg/day)	
8	8.9		17	
28	5.8		17	
56	5.1		17	
84	5.4		17	
112	6.1		17	
	Lower Lead	Higher Lead	Lower Lead	Higher Lead
140	6.2	9.3	16	61
168	7.0	12.1	16	61
196	7.2	14.4	16	61

Source: Ryu et al. (1983).

11.4.2.1.2 Rabinowitz study. This study on male adults was described in Section 11.4.1 and in Chapter 10, where ingestion experiments were analyzed in more detail (Rabinowitz et al., 1980). As in other studies, the fraction of ingested stable isotope lead tracers absorbed into the blood was much lower when lead was consumed with meals (10.3 ± 2.2 percent) than between meals (35 ± 13 percent). Lead nitrate, lead sulfide and lead cysteine as carriers made little difference. The much higher absorption of lead on an empty stomach implies greater significance of lead ingestion from leaded paint and from dust and soil when consumed between meals, as seems likely to be true for children.

11.4.2.1.3 Hubermont study. Hubermont et al. (1978) conducted a study of pregnant women living in rural Belgium because their drinking water was suspected of being lead contaminated. This area was known to be relatively free of air pollution. Seventy pregnant women were

recruited and were asked to complete a questionnaire. Information was obtained on lifetime residence history, occupational history, smoking and drinking habits. First flush tap water samples were collected from each home with the water lead level determined by flameless atomic absorption spectrophotometry. Biological samples for lead determination were taken at delivery. A venipuncture blood sample was collected from the mother as was a fragment of the placenta. An umbilical cord blood sample was used to estimate the newborn's blood lead status.

For the entire population, first flush tap water samples ranged from 0.2 to 1228.5 µg/l. The mean was 109.4 while the median was 23.2. The influence of water lead on the blood lead of the mother and infants was examined by categorizing the subjects on the basis of the lead level of the water sample, below or above 50 µg/l. Table 11-36 presents the results of this study. A significant difference in blood lead levels of mothers and newborns was found for the water lead categories. Placenta lead levels also differed significantly between water lead groups. The fitted regression equation of blood lead level for mothers is given in summary Table 11-42.

11.4.2.1.4 Sherlock study. Sherlock et al. (1982) reported a study from Ayr, Scotland, which considered both dietary and drinking water lead exposures for mothers and children living in the area. In December 1980, water lead concentrations were determined from kettle water from 114 dwellings in which the mother and child lived less than 5 years. The adult women had venous blood samples taken in early 1981 as part of a European Economic Community (EEC) survey on blood lead levels. A duplicate diet survey was conducted on a random sample of these 114 women stratified by kettle water lead levels.

A study population of 11 mothers with infants less than 4 months of age agreed to participate in the infant survey. A stratified sample of 31 of 47 adult volunteers was selected to participate in the duplicate diet study.

Venous blood samples for adults were analyzed for lead immediately before the duplicate diet study; in some instances additional samples were taken to give estimates of long term exposure. Venous samples were taken from the infants immediately after the duplicate diet week. Blood lead levels were determined by AAS with graphite furnace under good quality control. Two other laboratories analyzed each sample by different methods. The data reported are based on the average value of the three methods.

Dietary intakes for adults and children were quite different; adults had higher intakes than children. Almost one third of the adults had intakes greater than 3 mg/week while only 20 percent of the infants had that level of intake. Maximum values were 11 mg/week for adults and 6 mg/week for infants.

The observed blood lead values in the dietary study had the following distributions:

	>20 µg/dl	>30 µg/dl	>35 µg/dl
Adults	55%	16%	2%
Infants	100%	55%	36%
EEC Directive	50%	10%	2%

TABLE 11-36. INFLUENCE OF LEVEL OF LEAD IN WATER ON BLOOD LEAD LEVEL IN BLOOD AND PLACENTA

Comparison Group	Water Level	Mean	Median	Range	Significance
Age (Years)	Low**	25.6	24	18-41	NS*
	High***	26.3	25	20-42	
Pb-B mother (µg/dl)	Low	10.6	9.9	5.1-21.6	<0.005
	High	13.8	13.1	5.3-26.3	
Pb-B newborn (µg/dl)	Low	8.8	8.5	3.4-24.9	<0.001
	High	12.1	11.9	2.9-22.1	
Pb placenta (µg/100 g)	Low	9.7	8.2	4.4-26.9	<0.005
	High	13.3	12.0	7.1-28	
Water Pb (µg/l)	Low	11.8	6.3	0.2-43.4	
	High	247.4	176.8	61.5-1228.5	

Source: Hubermont et al. (1978)

*NS means not significant

**Water Lead <50 µg/l

***Water Lead >50 µg/l

Table 11-37 presents the crosstabulation of drinking water lead and blood lead level for the 114 adult women in the study. A strong trend of increasing blood lead levels with increasing drinking water lead levels is apparent. A curvilinear regression function fits the data better than a linear one. A similar model including weekly dietary intake was fitted to the data for adults and infants. These models are in summary Tables 11-41 and 11-44.

The researchers also developed a linear model for the relationship between dietary intake and drinking water lead. The equation indicates that, when the concentration of lead in water was about 100 µg/l, approximately equal amounts of lead would be contributed to the total

TABLE 11-37. BLOOD LEAD AND KETTLE WATER LEAD CONCENTRATIONS FOR ADULT WOMEN LIVING IN AYR

Blood lead µg per 100 ml	Water lead (µg/l)							
	<10	11-99	100-299	300-499	500-999	1000-1499	>1500	Total
<10	8	5						13
11-15	4	7	3	2			1	17
16-20	1	3	12	3	3			22
21-25		4	9	7	5			25
26-30			2	4	4	2		12
31-35			2	1	2	2	3	10
36-40				1	1	1	1	4
>40				1	4	3	3	11
Total	13	19	28	19	19	8	8	114

week's intake from water and from the diet; as water lead concentrations increase from this value, the principal contributor would be water.

11.4.2.1.5 Central Directorate on Environmental Pollution study. The United Kingdom Central Directorate on Environmental Pollution (1982) studied the relationship between blood lead level and dietary and drinking water lead in infants. Subjects were first recruited by soliciting participation of all pregnant women attending two hospitals and residing within a single water distribution system. Each woman gave a blood sample and a kettle water sample. The women were then allocated to one of six potential study groups based on the concentration of water lead.

At the start of the second phase (duplicate diet) a total of 155 women volunteered (roughly 17 to 32 per water lead level category). During the course of the study, 24 mothers withdrew; thus a final study population of 131 mothers was achieved.

At 13 weeks of age, duplicate diet for a week's duration was obtained for each infant. Great care was exerted to allow collection of the most accurate sample possible. Also, at this time a variety of water samples were collected for subsequent lead analysis.

Blood samples were collected by venipuncture from mothers before birth, at delivery, and about the time of the duplicate diet. A specimen was also collected by venipuncture from the infant at the time of the duplicate diet. The blood samples were analyzed for lead by graphite furnace AAS with deuterium background correction. Breast milk was analyzed analogously to the blood sample after pretreatment for the different matrix. Water samples were analyzed by flame atomic absorption. Food samples were analyzed after ashing by flameless atomic absorption.

Both mothers and infants exhibited increased lead absorption by EEC directive standards. The infants generally had higher blood leads than the mothers. However, in neither population was there evidence of substantial lead absorption.

Water lead samples ranged from less than 50 µg/l to greater than 500 µg/l, which was expected due to the sampling procedure used. First draw samples tended to be higher than the other samples. The composite kettle samples and the random daytime samples taken during the duplicate diet week were reasonably similar: 59 percent of the composite kettle samples contained up to 150 µg/l as did 66 percent of the random daytime samples.

Lead intakes from breast milk were lower than from duplicate diets. The lead intakes estimated by duplicate diet analysis ranged from 0.04 mg/week to 3.4 mg/week; about 1/4 of the diets had intakes less than 1.0 mg/week. The minimum intakes were truncated, as the limit of detection for lead was 10 µg/kg and the most common diets weighed 4 kg or more.

The authors used both linear and cube root models to describe their data. Models relating blood lead levels of infants to dietary intake are in Table 11-41. Models relating blood lead levels for both mothers and infants to first flush water lead levels and running water lead levels are in Tables 11-43 and 11-44, respectively. In most cases, the nonlinear (cubic) model provided the best fit. Figure 11-15 illustrates the fit for the two models showing infant blood lead levels vs. dietary lead intake.

11.4.2.1.6 Pocock study. Pocock et al. (1983) have recently reported an important study examining the relationship in middle aged men of blood lead level and water lead levels. Men aged 40 to 59 were randomly selected from the registers of general practices located in 24 British towns. Data were obtained between January 1978 and June 1980.

Blood lead levels were obtained on 95 percent of the 7378 men originally selected. The levels were determined by microatomic absorption spectrophotometry. A strict internal and external quality control program was maintained on the blood lead determinations for the entire study period. Tap water samples were obtained on a small subset of the population. About 40 men were chosen in each of the 24 towns to participate in the water study. First draw samples were collected by the subjects themselves, while a grab daytime and flushed sample were collected by study personnel. These samples were analyzed by several methods of AAS depending on the concentration range of the samples.

Blood lead and water lead levels were available for a total of 910 men from 24 towns. Table 11-38 displays the association between blood lead levels and water lead levels. Blood lead levels nearly doubled from the lowest to highest water lead category.

The investigators analyzed their data further by examining the form of the relationship between blood and water lead. This was done by categorizing the water lead levels into nine intervals of first draw levels. The first group (<6 µg/l) had 473 men while the remaining

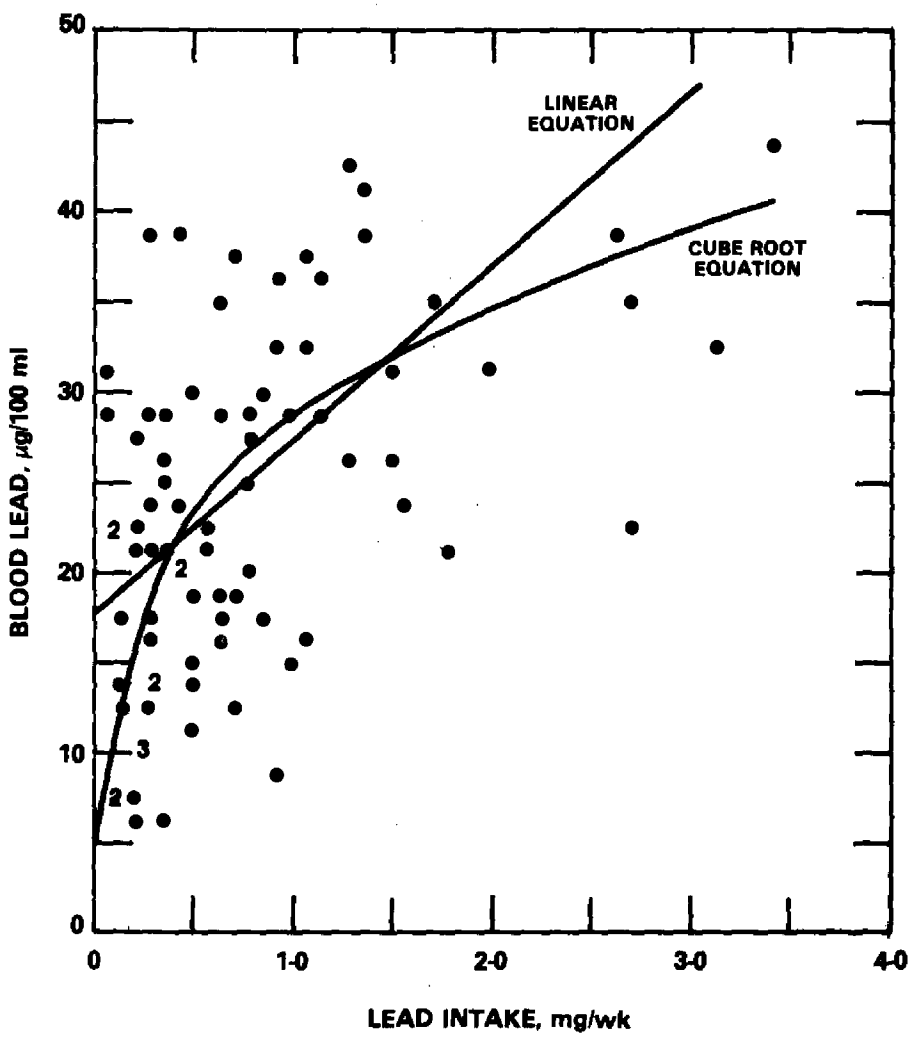

Figure 11-15. Blood-lead concentrations versus weekly lead intake for bottle-fed infants.

TABLE 11-38. RELATIONSHIP OF BLOOD LEAD (μg/dl) AND WATER LEAD (μg/dl) IN 910 MEN AGED 40-59 FROM 24 BRITISH TOWNS

First Draw Water Lead (μg/l)	Number of Men	Mean Blood Lead (μg/dl)	Standard Deviation	% with Blood Lead >35 μg/dl
<50	789	15.06	5.53	0.7
50-99	69	18.90	7.31	4.3
100-299	40	21.65	7.83	7.5
≥300	12	34.19	15.27	41.7
Total	910	15.89	6.57	1.9
Daytime Water Lead (μg/l)				
<50	845	15.31	5.64	0.7
50-99	36	19.62	7.89	8.3
100-299	23	24.78	9.68	17.4
≥300	5	39.78	15.87	60.0
Total	909	15.85	6.44	1.8

Source: Pocock et al. (1983).

eight intervals had ~ 50 men each. Figure 11-16 presents the results of this analysis. "The impression is that mean blood lead increases linearly with first draw water lead except for the last group with very high water concentrations." The regression line shown in the figure is only for men less than 100 μg/l, and is given in Table 11-43. A separate regression was done for the 49 men whose water lead exposures were greater than 100 μg/l. The slope for the second line was only 23 percent of the first line.

Additional analyses were done examining the possible influence of water hardness on blood lead levels. A strong negative relationship (r = -0.67) was found between blood lead level and water hardness. There is a possibility that the relationship between blood lead and water hardness was due to the relationship of water hardness and water lead. It was found that a relationship with blood lead and water hardness still existed after controlling for water lead level.

The authors come to the following conclusion regarding the slope of the relationship between blood lead and water lead:

> This study confirms that the relation is not linear at higher levels. Previous research had suggested a power function relationship--for example, blood lead increases as the cube root of water lead. Our data, based on a large and more representative sample of men, do not agree with such a curve, particularly at low concentrations of water lead.

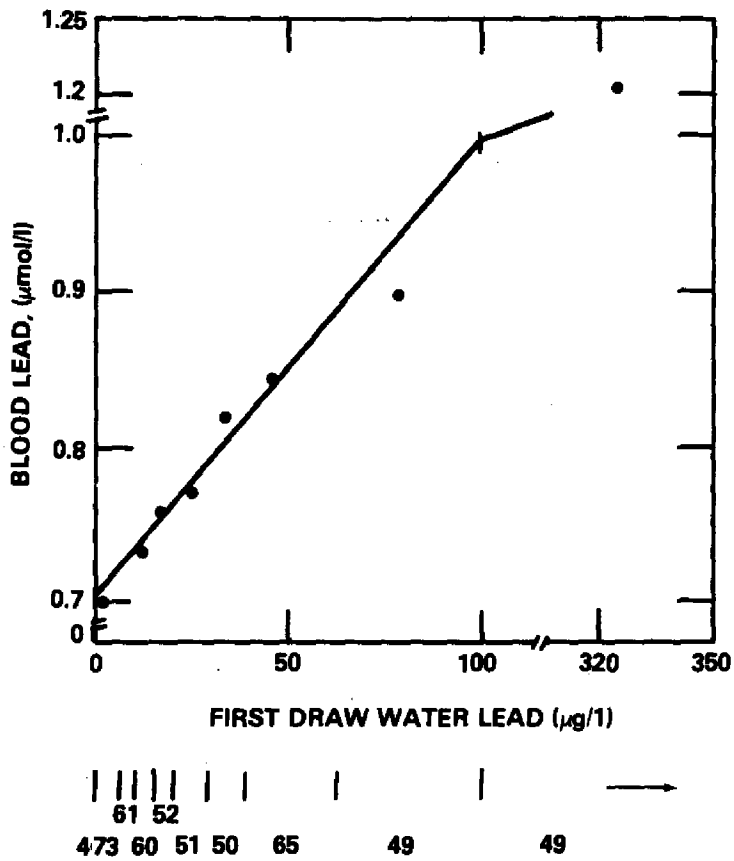

Figure 11-16. Mean blood lead for men grouped by first draw water concentration.

Source: Pocock et al. (1983).

11.4.2.2. Lead Ingestion from Experimental Dietary Supplements.

11.4.2.2.1 Kehoe study. Experimental studies have been used to study the relationship of food lead and blood lead levels. Gross (1981) reanalyzed the results of Kehoe. Oral doses of lead included 300, 1000, 2000, and 3000 µg/day. Each subject had a control period and an exposure period. Some also had a post-exposure period. Blood samples were collected by venipuncture and analyzed by spectrographic and dithizone methods during the study years. The ingestion doses were in addition to the regular ingestion of lead from the diet. The results of the dose response analysis for blood lead concentrations are summarized in Table 11-39.

Both subjects MR and EB had long exposure periods, during which time their blood lead levels increased to equilibrium averages of 53 and 60 µg/dl, respectively. The exposure for IF was terminated early before his blood lead had achieved equilibrium. No response in blood lead was seen for subject SW whose supplement was 300 µg/day.

TABLE 11-39. DOSE RESPONSE ANALYSIS FOR BLOOD LEAD LEVELS IN THE KEHOE STUDY AS ANALYZED BY GROSS (1981)

Subject	Added lead (µg/day)	Difference from control: Diet (µg/day)	Feces (µg/day)	Urine (µg/day)	Blood (µg/dl)
SW	300	308	208	3	-1
MR	1000	1072	984	55	17
EB	2000	1848	1547	80	33
IF*	3000	2981	2581	49	19

*Subject did not reach equilibrium.

11.4.2.2.2 Stuik study. Stuik (1974) administered lead acetate in two dose levels (20 and 30 µg/kg body weight·day) to volunteers. The study was conducted in two phases. The first phase was conducted for 21 days during February-March 1973. Five males and five females aged 18-26 were exposed to a daily dose of 20 µg Pb^{2+}/kg of body weight. Five males served as controls. In the second phase, five females received 20 µg Pb^{2+}/kg body weight and five males received 30 µg Pb^{2+}/kg body weight. Five females served as controls. Pre-exposure values were established during the week preceding the exposures in both phases. Blood lead levels were determined by Hessel's method.

The results of phase I for blood lead levels are presented in Figure 11-17. Blood lead levels appeared to achieve an equilibrium after 17 days of exposure. Male blood lead levels went from 20.6 µg/g to 40.9 µg/g while females went from 12.7 to 30.4 µg/g. The males seemed to respond more to the same body weight dose.

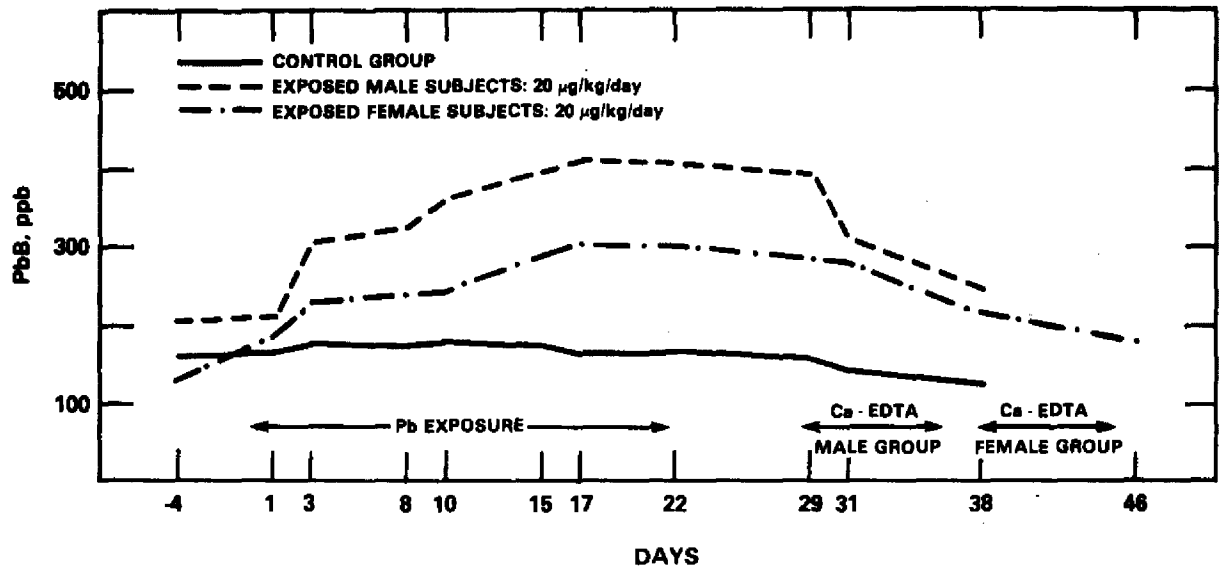

Figure 11-17. Average PbB levels, Exp. I.

Source: Stuik (1974).

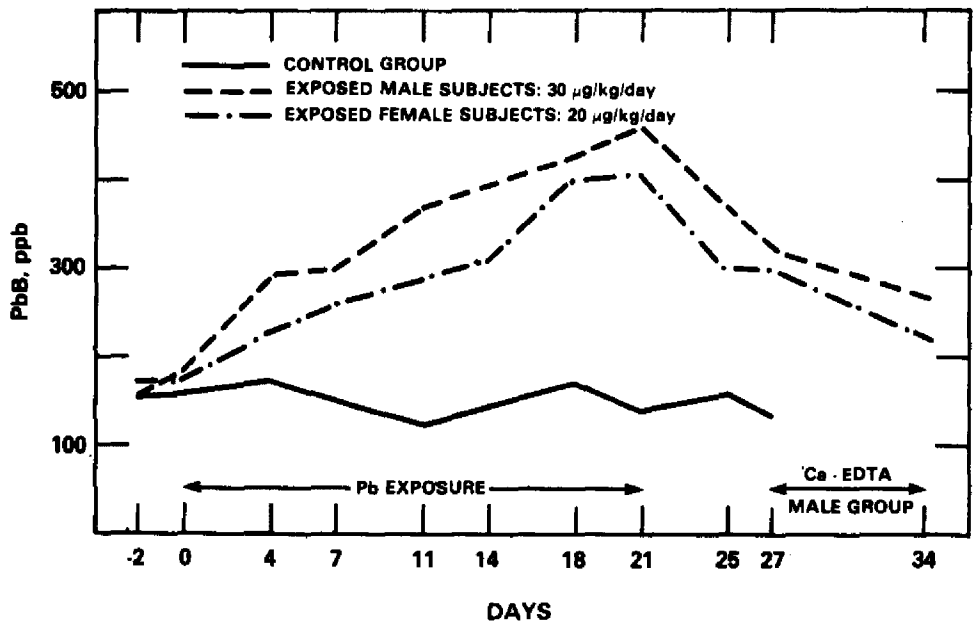

Figure 11-18. Average PbB levels, Exp. II.

Source: Stuik (1974).

In phase II, males were exposed to a higher lead dose (30 μg/kg·day). Figure 11-19 displays these results. Male blood lead rose higher than in the first study (46.2 vs. 40.9 μg/g); furthermore, there was no indication of a leveling off. Females also achieved a higher blood lead level (41.3 vs. 30.4), which the author could not explain. The pre-exposure level, however, was higher for the second phase than the first phase (12.7 vs. 17.3 μg/g).

11.4.2.2.3 Cools study. Cools et al. (1976) extended the research of Stuik (1974) by randomly assigning 21 male subjects to two groups. The experimental group was to receive a 30 μg/kg body weight dose of oral lead acetate long enough to achieve a blood lead level of 30.0 μg/g, when the lead dose would be adjusted downward to attempt to maintain the subjects at a blood lead level of 40.0 μg/g. The other group received a placebo.

In the pre-exposure phase, blood lead levels were measured three times, while during exposure they were measured once a week, except for the first three weeks when they were determined twice a week. Blood lead was measured by flame AAS according to the Westerlund modification of Hessel's method.

Pre-exposure blood lead values for the 21 volunteers averaged 172 ppb. The effect of ingestion of lead acetate on blood lead is displayed in Figure 11-19. After 7 days mean blood lead levels had increased from 17.2 to 26.2 μg/g. The time to reach a blood lead level of 35.0 μg/g took 15 days on the average (range 7-40 days).

11.4.2.2.4 Schlegel study. Schlegel and Kufner (1979) report an experiment in which two subjects received daily oral doses of 5 mg Pb^{+2} as an aqueous solution of lead nitrate for 6 and 13 weeks, respectively. Blood and urine samples were taken. Blood lead uptake (from 16 to 60 μg/dl in 6 weeks) and washout were rapid in subject HS, but less so in subject GK (from 12 to 29 μg/dl in 6 weeks). Time series data on other heme system indicators (FEP, δ-ALA-D, δ-ALA-U, coproporphyrin III) were also reported.

11.4.2.2.5 Chamberlain study. This study (Chamberlain et al., 1978) was described in Section 11.4.1, and in Chapter 10. The ingestion studies on six subjects showed that the gut absorption of lead was much higher when lead was ingested between meals. There were also differences in absorption of lead chloride and lead sulfide.

11.4.2.3 Inadvertent Lead Ingestion from Lead Plumbing.

11.4.2.3.1 Early studies. Although the use of lead piping has been largely prohibited in recent construction, occasional episodes of poisoning from this lead source still occur. These cases most frequently involve isolated farms or houses in rural areas, but a surprising urban episode was revealed in 1972 when Beattie et al. (1972a,b) showed the seriousness of the situation in Glasgow, Scotland, which had very pure but soft drinking water as its source. The researchers demonstrated a clear association between blood lead levels and inhibition of the enzyme ALA-D in children living in houses with (1) lead water pipes and lead water tanks,

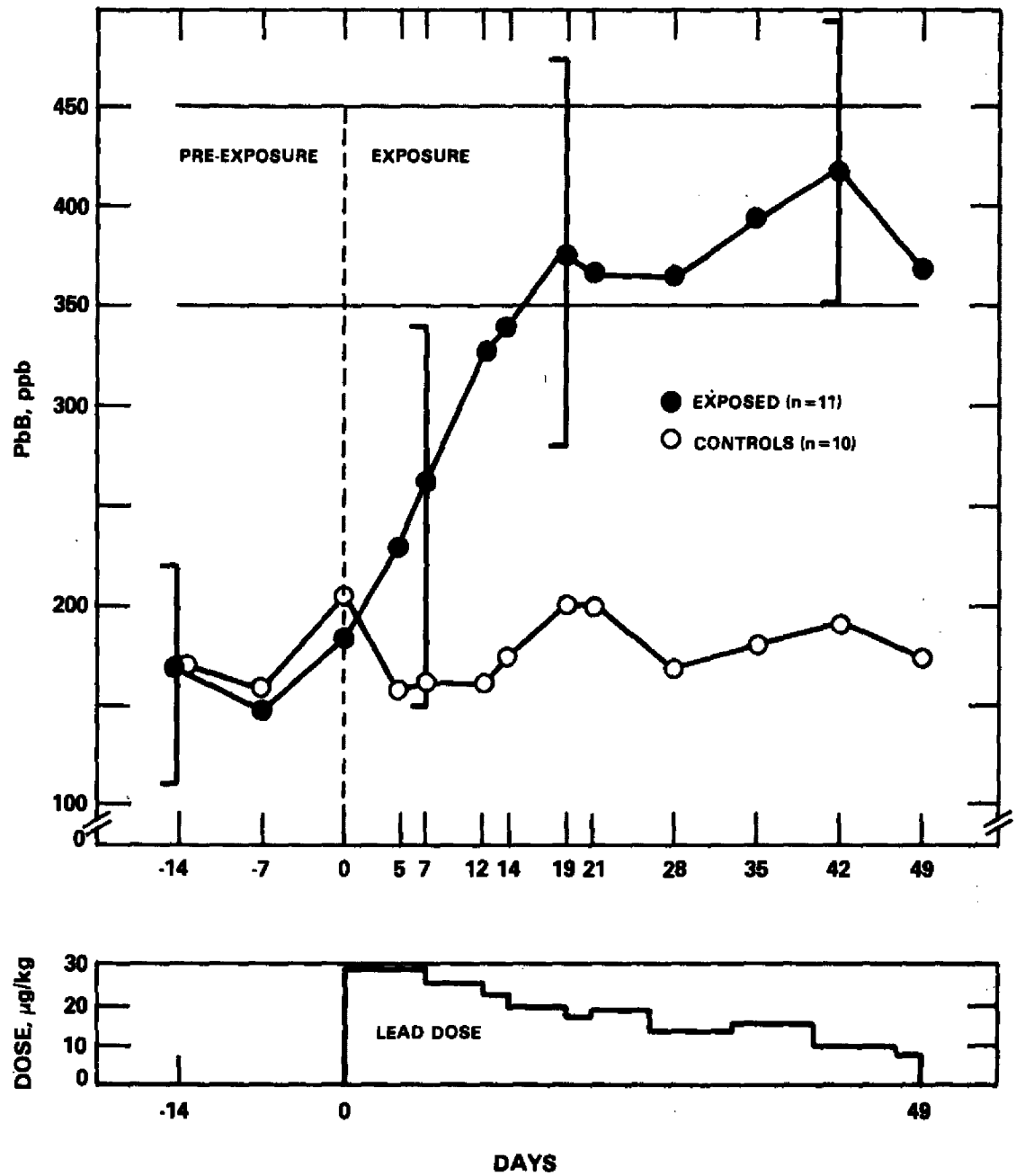

Figure 11-19. Lead in blood (mean values and range) in volunteers. In the lower curve the average daily lead dose of the exposed group is shown.

Source: Cools (1976).

(2) no lead water tank but with more than 60 ft of lead piping and (3) less than 60 ft of lead piping. The mean lead content of the water as supplied by the reservoir was 17.9 µg/l; those taken from the faucets of groups 1, 2 and 3 were 934, 239 and 108 µg/l, respectively.

Another English study (Crawford and Crawford, 1969) showed a clear difference between the bone lead contents of the populations of Glasgow and London, the latter having a hard, nonsolvent water supply.

In a study of 1200 blood donors in Belgium (DeGraeve et al., 1975), persons from homes with lead piping and supplied with corrosive water had significantly higher blood lead levels.

11.4.2.3.2 Moore studies. M. R. Moore and colleagues have reported on several studies relating blood lead levels to water lead levels. Moore (1977) studied the relationship between blood lead level and drinking water lead in residents of a Glasgow tenement. The tenement was supplied with water from a lead-lined water tank carried by lead piping. Water samples were collected during the day. Comparative water samples were collected from houses with copper pipes and from 15 lead plumbed houses. Blood samples were taken wherever possible from all inhabitants of these houses. The data indicated that if a house has lead lined pipes, it is almost impossible to reach the WHO standard for lead in water. Linear regression equations relating blood lead levels to first flush and running water lead levels are in Tables 11-43 and 11-44.

Moore et al. (1977) also reported the analysis of blood lead and water lead data collected over a four year period for different sectors of the Scottish population. The combined data showed consistent increases in blood lead levels as a function of first draw water lead, but the equation was nonlinear at the higher range. The water lead values were as high as 2000 µg/l. The fitted regression equation for the 949 subjects is in Table 11-43.

Moore et al. (1981a,b) reported a study of the effectiveness of control measures for plumbosolvent water supplies. In autumn and winter of 1977, they studied 236 mothers aged 17 to 37 in a post-natal ward of a hospital in Glasgow with no historical occupational exposure. Blood lead and tap water samples from the home were analyzed for lead by AAS under a quality control program.

A skewed distribution of blood lead levels was obtained with a median value of 16.6 µg/dl; 3 percent of the values exceeding 41 µg/dl. The geometric mean was 14.5 µg/dl. A curvilinear relationship between blood lead level and water lead level was found. The log of the maternal blood lead varied as the cube root of both first flush and running water lead concentrations. In Moore et al. (1979) further details regarding this relationship are provided. Figure 11-20 presents the observed relationship between blood lead and water lead.

In April 1978 a closed loop lime dosing system was installed. The pH of the water was raised from 6.3 to 7.8. Before the treatment, more than 50 percent of random daytime water samples exceeded 100 µg of Pb/l, the WHO standard. After the treatment was implemented, 80

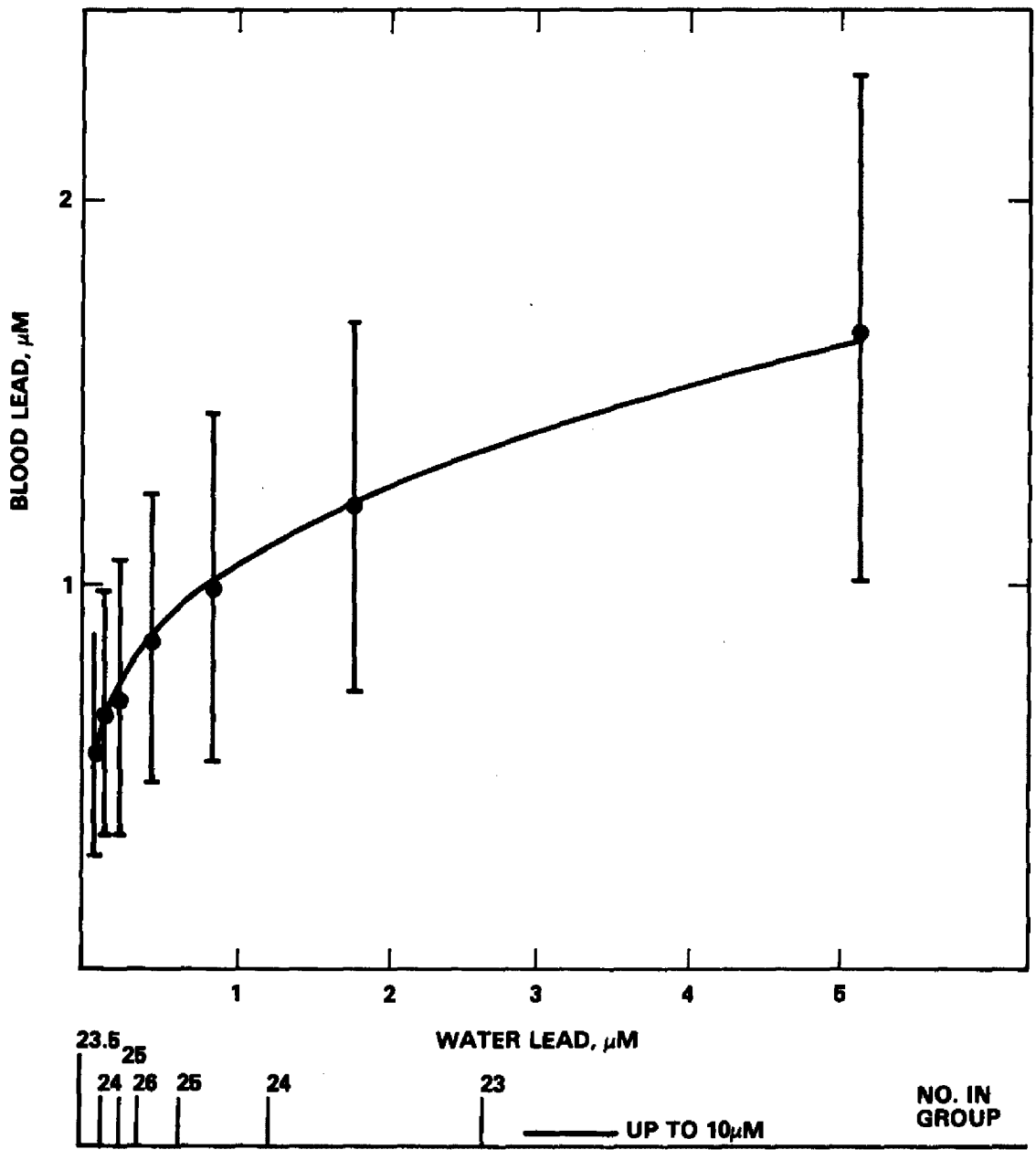

Figure 11-20. Cube root regression of blood lead on first flush water lead. This shows mean ± S.D. of blood lead for pregnant women grouped in 7 intervals of first flush water lead.

percent of random samples were less than 100 µg/l. It was found, however, that the higher pH was not maintained throughout the distribution system. Therefore, in August 1980, the pH was raised to 9 at the source, thereby maintaining the tap water at 8. At this time more than 95 percent of random daytime samples were less than 100 µg/l.

In the autumn and winter of 1980, 475 mothers from the same hospital were studied. The median blood lead was 6.6 µg/dl and the geometric mean was 8.1 µg/dl. Comparison of the frequency distributions of blood lead between these two blood samplings show a remarkable drop. No other source of lead was thought to account for the observed change.

11.4.2.3.3 Thomas study. Thomas et al. (1979) studied women and children residing on two adjacent housing estates. One estate was serviced by lead pipes for plumbing while the other was serviced by copper pipe. In five of the homes in the lead pipe estate, the lead pipe had been replaced with copper pipe. The source water is soft, acidic and lead-free.

Water samples were collected from the cold tap in the kitchen in each house on three occasions at two-week intervals. The following water samples were collected: daytime - first water out of tap at time of visit; running - collected after tap ran moderately for 5 minutes after the daytime sample; and first flush - first water out of tap in morning (collected by residents). Lead was analyzed by a method (unspecified in report) that was reportedly under quality control.

Blood samples were collected from adult females (2.5 ml venipuncture) who spent most of the time in the home and from the youngest child (capillary sample). Blood samples were analyzed for lead by a quality controlled unspecified method. Blood lead levels were higher in the residents of the lead estate homes than in the residents of the copper estate homes. Median levels for adult females were 39 µg/dl and 14.5 µg/dl for the lead and copper estate homes, respectively. Likewise, children's blood lead levels were 37 µg/dl and 16.6 µg/dl, respectively. Water lead levels were substantially higher for the lead estate than for the copper estate. This was true for all three water samples.

The researchers then monitored the effectiveness of replacing the lead pipe on reducing both exposure to lead in drinking water and ultimately blood lead levels. This monitoring was done by examining subsamples of adult females for up to 9 months after the change was implemented. Water lead levels became indistinguishable from those found in the copper estate homes. Blood lead levels declined about 30 percent after 3 to 4 months and 50 percent at 6 and 9 months. At 6 months the blood lead levels reached those of women living in the copper estates. A small subgroup of copper estate females was also followed during this time. No decline was noted among them. Therefore, it was very likely that the observed reduction in blood lead levels among the other women was due to the changed piping.

The researchers then analyzed the form of the relationship between blood lead levels and water lead levels. They tried several different shapes for the regression line. Curvilinear models provided better fits. Figure 11-21 depicts the scatter diagram of blood lead and water lead. An EPA analysis of the data is in Table 11-43.

A later publication by Thomas (1980) extended his earlier analysis. This more extensive analysis was limited to lead estate residents. Subjects who did not consume the first drawn water from the tap had significantly lower blood lead levels than those who did (10.4 µg/dl difference). No gradient was noted in blood lead levels with increasing water consumption. Furthermore, no gradient in blood lead levels was noted with total beverage consumption (tea ingestion frequency).

11.4.2.3.4 Worth study. In Boston, Massachusetts an investigation was made of water distribution via lead pipes. In addition to the data on lead in water, account was taken of socioeconomic and demographic factors as well as other sources of lead in the environment (Worth et al., 1981). Participants, 771 persons from 383 households, were classified into age groups of less than 6, 6 to 20, and greater than 20 years of age for analysis. A clear association between water lead and blood lead was apparent (Table 11-40). For children under 6 years of age, 34.6 percent of those consuming water with lead above the U.S. standard of 50 µg/l had a blood lead value greater than or equal to 35 µg/dl, whereas only 17.4 percent of those consuming water within the standard had blood lead values of greater than or equal to 35 µg/dl.

Worth et al. (1981) have published an extensive regression analysis of these data. Blood lead levels were found to be significantly related to age, education of head of household, sex and water lead exposure. Of the two types of water samples taken, standing grab sample and running grab sample, the former was shown to be more closely related to blood lead levels than the latter. Regression equations are given in Tables 11-43 and 11-44.

11.4.2.4 Summary of Dietary Lead Exposures Including Water. It is difficult to obtain accurate dose-response relationships between blood lead levels and lead levels in food or water. Dietary intake must be estimated by duplicate diets or fecal lead determinations. Water lead levels can be determined with some accuracy, but the varying amounts of water consumed by different individuals adds to the uncertainty of the estimated relationships.

Studies relating blood lead levels to dietary lead intake are compared in Table 11-41. Most of the subjects in the Sherlock et al. (1982) and United Kingdom Central Directorate on Environmental Pollution (1982) studies received quite high dietary lead levels (>300 µg/day). The fitted cubic equations give high slopes at lower dietary lead levels. On the other hand, the linear slope of the United Kingdom Central Directorate on Environmental Pollution (1982) study is probably an underestimate of the slope at lower dietary lead levels. For these

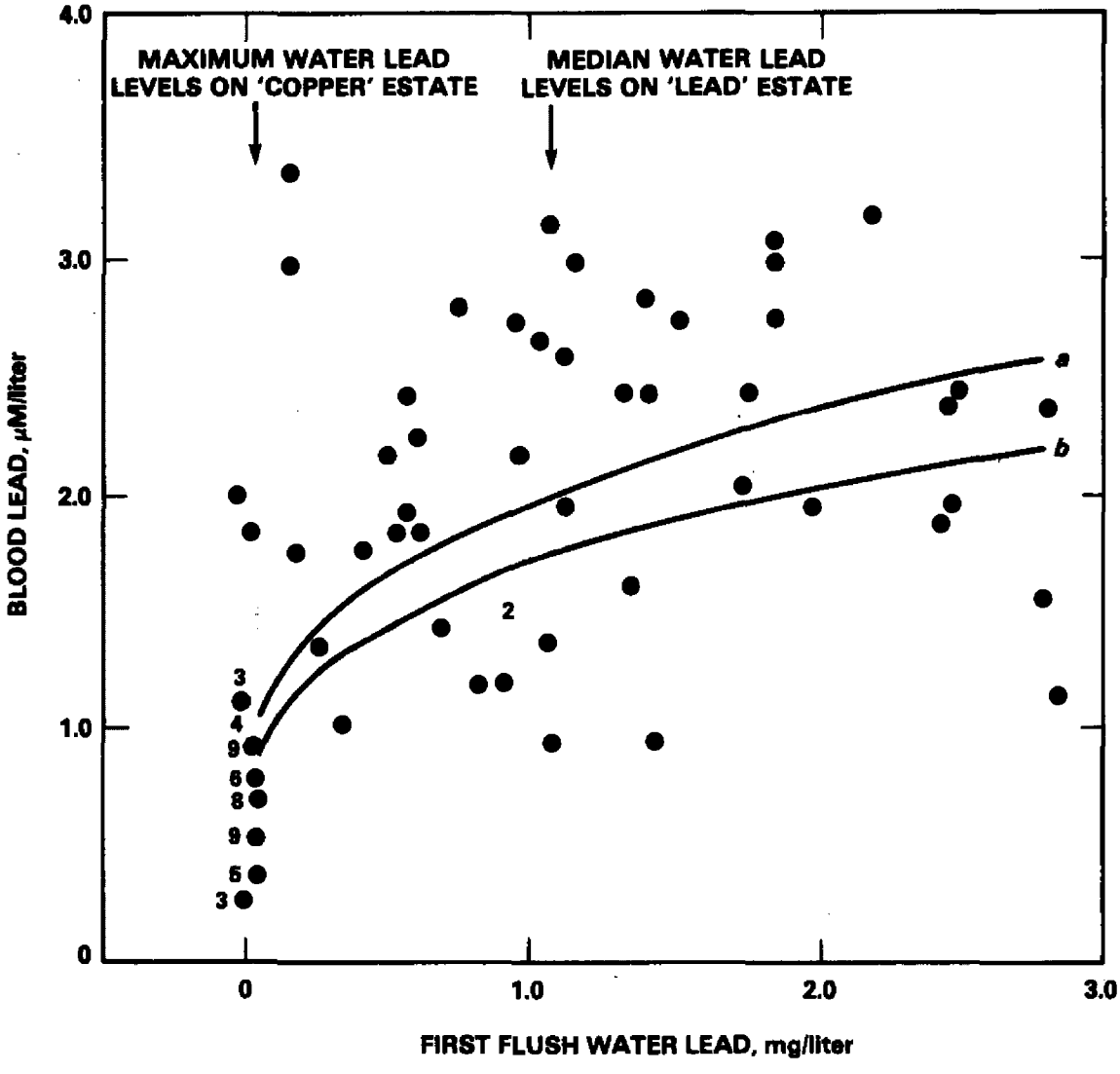

Figure 11-21. Relation of blood lead (adult female) to first flush water lead in combined estates. (Numbers are coincidental points: 9 = 9 or more.) Curve *a*, present data; curve *b*, data of Moore *et al.*

TABLE 11-40. BLOOD LEAD LEVELS OF 771 PERSONS IN RELATION TO LEAD CONTENT OF DRINKING WATER, BOSTON, MA

Blood lead levels, µg/dl	Persons consuming water (standing grab samples)				
	<50 µg Pb/l		≥50 µg Pb/l		
	No.	Percent	No.	Percent	Total
<35	622	91	68	77.3	690
≥35	61	9	20	22.7	81
Total	683	100	88	100.0	771

$\chi^2 = 14.35$; df = 1.

P <0.01.

Source: Worth et al. (1981).

reasons, the Ryu et al. (1983) study is the most believable, although it only applies to infants. Estimates for adults should be taken from the experimental studies or calculated from assumed absorption and half-life values.

The experimental studies are summarized in Table 11-42. Most of the dietary intake supplements were so high that many of the subjects had blood lead concentrations much in excess of 30 µg/dl for a considerable part of the experiment. Blood lead levels thus may not completely reflect lead exposure, due to the previously noted nonlinearity of blood lead response at high exposures. The slope estimates for adult dietary intake are about 0.02 µg/dl increase in blood lead per µg/day intake, but consideration of blood lead kinetics may increase this value greatly. Such values are a bit lower than those estimated from the population studies extrapolated to typical dietary intakes in Table 11-41, about 0.05 µg/dl per µg/day. The value for infants is much larger.

The studies relating first flush and running water lead levels to blood lead levels are in Tables 11-43 and 11-44, respectively. Many of the authors chose to fit cube root models to their data, although polynomial and logarithmic models were also used. Unfortunately, the form of the model greatly influences the estimated contributions to blood lead levels from relatively low water lead concentrations.

The models producing high estimated contributions are the cube root models and the logarithmic models. These models have a slope that approaches infinity as water lead concentrations approache zero. All other are polynomial models, either linear, quadratic or cubic. The slopes of these models tend to be relatively constant at the origin.

TABLE 11-41. STUDIES RELATING BLOOD LEAD LEVELS (μg/dl) TO DIETARY INTAKES (μg/day)

Study	Analysis	Model	R^2	Model D.F.	Estimated Blood lead at 0 H_2O Pb	Predicted blood lead contribution (μg/dl) for a given dietary intake (μg/day)			Slope from 100 to 200 μg/d., μg/dl per μg/d.
						100	200	300	
Sherlock et al. (1982) study of 31 adult women in Ayr	Sherlock et al. (1982)	$PBB = -1.4 + 3.6\sqrt[3]{PBD}$	0.52	2	-1.4	16.7	21.1	24.1	0.034
Sherlock et al. (1982) study of infants in Ayr combined with U.K. Central Directorate Study	Sherlock et al. (1982)	$PBB = 2.5 + 5.0\sqrt[3]{PBD}$	-	2	2.5	23.2	29.2	33.5	0.060
U.K. Central Directorate (1982) Study of infants in Glasgow	U.K. Central Directorate on Environmental Pollution (1982)	$PBB = 17.1 + .056(PBD)$ or $PBB = 3.9 + 4.6\sqrt[3]{PBD}$	0.39 0.43	2 2	17.1 3.9	5.6 21.4	11.2 26.9	16.8 30.8	0.056 0.053
Ryu et al. (1983) study of infants	EPA	$PBB = A + .16PBD$	-	1	-	16.0	32.0	48.0	0.16

TABLE 11-42. STUDIES INVOLVING BLOOD LEAD LEVELS (μg/dl) AND EXPERIMENTAL DIETARY INTAKES

Study	Subjects	Exposure	Form of Lead	Blood Lead		Slope* μg/dl per μg/d.
				Initial	Final	
Stuik (1974)	5 adult male students	20 μg Pb/kg/day - 21 d.	Lead acetate	20.6	40.9	0.017**,***
Study I	5 adult female students	20 μg Pb/kg/day - 21 d.	Lead acetate	12.7	30.4	0.018**,***
	5 adult male students	Controls - 21 d.	Placebo	20.6	18.4	-
Study II	5 adult female students	20 μg Pb/kg/day	Lead acetate	17.3	41.3	0.022
	5 adult male students	30 μg Pb/kg/day	Lead acetate	16.1	46.2	0.014
	5 adult female students	Controls	Placebo	~17.0	~17.0	-
Cools et al. (1976)	11 adult males	30 μg Pb/kg/day ~7 days	Lead acetate	17.2	26.2	0.027***
	10 adult males	Controls	Placebo		~19.0	-
Schlegel and Kufner (1979)	1 adult male	50 μg Pb/kg/day - 6 wk.	Lead nitrate	16.5	64.0	0.014
	1 adult male	70 μg Pb/kg/day -13 wk.	Lead nitrate	12.4	30.4	0.004****
Gross (1979)	1 adult male	300 μg/day	Lead acetate		-1	[0]
analysis of	1 adult male	1000 μg/day	Lead acetate		+17	0.017
Kehoe's	1 adult male	2000 μg/day	Lead acetate		+33	0.016
experiments	1 adult male	3000 μg/day	Lead acetate		+19	0.006*****

* Exposure (μg/d) = Exposure (μg/kg/day) x 70 kg for males, 55 kg for females. Slope = (Final - Initial Blood Lead)/Exposure (μg/d).

** Corrected for decrease of 2.2 μg/dl in control males.

*** Assumed mean life 40d. This increases slope estimate for short-term studies. Stuik Study I would be 0.042, 0.044 respectively for males, females.

**** Assumed limited absorption of lead.

***** Removed from exposure before equilibrium.

TABLE 11-43. STUDIES RELATING BLOOD LEAD LEVELS (μg/dl) TO FIRST-FLUSH WATER LEAD (μg/l)

Study	Analysis	Model	R^2	Model D.F.	Estimated Blood lead at 0 H_2O Pb	Predicted blood lead contribution (μg/dl for a given water lead (μg/l) 5	10	25	50
Worth et al. (1981) study of 524 subjects in greater Boston. Water leads (standing water) ranged from <13 to 1108 μg/l. Blood leads ranged from 6 to 71.	Worth et al. (1981)	ln (PBB) = 2.729 PBW - 4.699 $(PBW)^2$ + 2.116 $(PBW)^3$ + other terms for age, sex, education, dust (PBW is in mg/l)	0.18	14	20.5	0.3	0.6	1.4	2.7
	EPA	ln(PBB) = ln (40.69 PBW - 21.89 $(PBW)^2$ + other terms for age, sex, education, dust) (PBW is in mg/l)	0.18	11	21.1	0.2	0.4	1.0	2.1
Moore et al. (1979) study of 949 subjects from different areas of Scotland. Water leads were as high as 2000 μg/l.	Moore et al. (1979)	PBB = 11.0 + 2.36 $(PBW)^{1/3}$		2	11.0	4.0	5.1	6.9	8.7
Hubermont et al. (1978) study of 70 pregnant women in rural Belgium. Water leads ranged from 0.2 to 1228.5 μg/l. Blood leads ranged from 5.1 to 26.3 μg/dl.	Hubermont et al. (1978)	PBB = 9.62 + 0.756 ln (PBW)	0.14	2	8.4*	2.4	3.0	3.7	4.2
U.K. Central Directorate (1982) study of 128 mothers in greater Glasgow. Water leads ranged from under 50 μg/l (35%) to over 500 μg/l (11%). Blood leads ranged from under 5 μg/dl (2%) to over 35 μg/dl (5%).	U.K. Central Directorate on Environmental Pollution (1982)	PBB = 13.2 + 1.8 $(PBW)^{1/3}$	0.11	2	13.2	3.1	3.9	5.3	6.6
		PBB = 18.0 + 0.009 PBW	0.05	2	18.0	0.0	0.1	0.2	0.4
U.K. Central Directorate (1982) study of 126 infants (as above). Blood leads ranged from under 5 μg/dl (4%) to over 40 μg/dl (4%).	U.K. Central Directorate on Environmental Pollution (1982)	PBB = 9.4 + 2.4 $(PBW)^{1/3}$	0.17	2	9.4	4.1	5.2	7.0	8.8
		PBB = 17.1 + 0.018 PBW	0.12	2	17.1	0.1	0.2	0.4	0.9
Thomas et al. (1979) study of 115 adult Welsh females. Water leads ranged from <10 to 2800 μg/dl. Blood leads ranged from 5 to 65 μg/dl.	EPA	ln (PBB) = [14.9 + 0.041 PBW - 0.000012 $(PBW)^2$]	0.61	3	14.9	0.2	0.4	1.0	2.0
Moore (1977) study of 75 residents of a Glasgow tenement	Moore (1977)	PBB = 15.7 + 0.015 PBW	0.34	2	15.7	0.1	0.2	0.4	0.8
Pocock et al. (1983) study of 7735 men aged 40-59 in Great Britain. Water leads restricted to <100 μg/l.	Pocock et al. (1983)	PBB = 14.48 + 0.062 PBW		2	14.5	0.3	0.6	1.6	3.1

*minimum water lead of 0.2 μg/dl used instead of 0.

TABLE 11-44. STUDIES RELATING BLOOD LEAD LEVELS (μg/dl) TO RUNNING WATER LEAD (μg/l)

Study	Analysis	Model	R^2	Model D.F.	Estimated Blood lead at 0 H_2O Pb	Predicted blood lead contribution (μg/dl) for a given water lead (μg/l) 5	10	25	50
Worth et al. (1981) study of 524 subjects in greater Boston. Water leads ranged from <13 to 208 μg/dl. Blood leads ranged from 6 to 71.	EPA	ln (PBB) = (0.0425 PBW + other terms for age, sex, education, and dust)	0.153	10	21.3	0.2	0.4	1.1	2.1
Worth et al. (1981) study restricted to 390 subjects aged 20 or older.	U.S. EPA (1980)	$PBB = 14.33 + 2.541\ (PBW)^{1/3}$	0.023	2	14.3	4.4	5.4	7.4	9.4
	EPA	EPA ln (PBB) = ln (18.6 + 0.071 PBW)	0.028	2	18.6	0.4	0.7	1.8	3.6
	EPA	ln (PBB) = ln (0.073 PBW + other terms for sex, education, and dust)	0.153	7	18.8	0.4	0.7	1.8	3.7
Worth et al. (1981) study restricted to 249 females ages 20 to 50.	U.S. EPA (1980)	$PBB = 13.38 + 2.487\ (PBW)^{1/3}$	0.030	2	13.4	4.3	5.4	7.3	9.2
	EPA	ln (PBB) = ln (17.6 + 0.067 PBW)	0.032	2	17.6	0.3	0.7	1.7	3.4
	EPA	ln (PBB) = (0.067 PBW + other terms for education and dust)	0.091	6	17.6	0.3	0.7	1.7	3.4
U.K. Central Directorate (1982) study of 128 mothers in greater Glasgow. Water leads ranged from under 50 μg/l (61%) to over 500 μg/dl (5%). Blood leads ranged from under 5 μg/dl (2%) to over 35 μg/dl (5%).	U.K. Central Directorate on Environmental Pollution (1982)	$PBB = 12.8 + 1.8\ (PBW)^{1/3}$	0.12	2	12.8	3.1	3.9	5.3	6.6
		PBB = 18.1 + .014 PBW	0.06	2	18.1	0.1	0.1	0.4	0.7
U.K. Central Directorate (1982) study of 126 infants in greater Glasgow. Water leads ranged from under 50 μg/l (61%) to over 500 μg/dl (5%). Blood leads ranged from under 5 μg/dl (4%) to over 40 μg/dl (4%).	U.K. Central Directorate on Environmental Pollution (1982)	$PBB = 7.6 + 2.3\ (PBW)^{1/3}$	0.22	2	7.6	3.9	5.0	6.7	8.5
		PBB = 16.7 + 0.033 PBW	0.12	2	16.7	0.2	0.3	0.8	1.6
Moore (1977) study of 75 residents of a Glasgow tenement.	Moore (1977)	PBB = 16.6 + 0.02 PBW	0.27	2	16.6	0.1	0.2	0.5	1.0
Sherlock et al. (1982) study of 114 adult women. Blood leads ranged <5 to >61 μg/dl. Kettle water leads ranged from <10 to >2570 μg/l.	Sherlock et al. (1982)	$PBB = 4.7 + 2.78\ (PBW)^{1/3}$	0.56	2	4.7	4.8	6.0	8.1	10.2

The problem of determining the most appropriate model(s) is essentially equivalent to the low dose extrapolation problem, since most data sets estimate a relationship that is primarily based on water lead values from 50 to 2000 µg/dl. The only study that determines the relationship based on lower water lead values (<100 µg/l) is the Pocock et al. (1983) study. The data from this study, as well as the authors themselves, suggest that in this lower range of water lead levels, the relationship is linear. Furthermore, the estimated contributions to blood lead levels from this study are quite consistent with the polynomial models from other studies, such as the Worth et al. (1981) and Thomas et al. (1979) studies. For these reasons, the Pocock et al. (1983) slope of 0.06 is thought to represent the current best estimate. The possibility still exists, however, that the higher estimates of the other studies may be correct in certain situations, especially at higher water lead levels (>100 µg/l).

11.4.3 Studies Relating Lead in Soil and Dust to Blood Lead

The relationship of exposure to lead contained in soil and house dust, and the amount of lead absorbed by humans, particularly children, has been the subject of scientific investigation for some time (Duggan and Williams, 1977; Barltrop, 1975; Creason et al., 1975; Barltrop et al., 1974; Roberts et al., 1974; Sayre et al., 1974; Ter Haar and Aronow, 1974; Fairey and Gray, 1970). Duggan and Williams (1977) published an assessment of the risk of increased blood lead resulting from the ingestion of lead in dust. Some of these studies have been concerned with the effects of such exposures (Barltrop, 1975; Creason et al., 1975; Barltrop et al., 1974; Roberts et al., 1974; Fairey and Gray, 1970); others have concentrated on the means by which the lead in soil and dust becomes available to the body (Sayre et al., 1974; Ter Haar and Aronow, 1974).

11.4.3.1 Omaha Nebraska Studies. The Omaha studies were described in Section 11.4.1.7. Soil samples were 2-inch cores halfway between the building and the lot line. Household dust was collected from vacuum cleaner bags. The following analysis was provided courtesy of Dr. Angle. The model is also described in Section 11.4.1.8, and provided the following coefficients and standard errors:

Factor	Coefficient	Asymptotic Standard Error
Intercept (µg/dl)	15.67	0.398
Air lead (µg/m^3)	1.92	0.600
Soil lead (mg/g)	6.80	0.966
House dust (mg/g)	7.18	0.900

Multiple R^2 = 0.198
Sample size = 1075
Residual standard deviation = 0.300 (geometric standard deviation = 1.35)

11.4.3.2 The Stark Study. EPA analyses of data from children in New Haven (Stark et al., 1982) found substantial evidence for dust and soil lead contributions to blood lead, as well as evidence for increased blood lead due to decreased household cleanliness. These factors are somewhat correlated with each other, but the separate roles of increased concentration and cleanliness could be distinguished. The fitted models were summarized earlier (Section 11.3.6.1).

11.4.3.3 The Silver Valley/Kellogg Idaho Study. The Silver Valley Kellogg Idaho study was discussed in section 11.4.1.6. Yankel et al. (1977) showed that lead in both soil and dust was independently related to blood lead levels. In their opinion, 1000 μg/g soil lead exposure was cause for concern. Walter et al. (1980) showed that children aged 3 through 6 showed the strongest relationship between soil lead and blood lead, but 2-year olds and 7-year olds also had a significant relationship (Table 11-24). The slope of 1.1 for soil lead (1000 μg/g) to blood lead (μg/dl) represents an average relationship for all ages.

The Silver Valley-Kellogg Idaho study also gave some information on house dust lead, although this data was less complete than the other information. Regression coefficients for these data are in Tables 11-24 and 11-25. In spite of the correlation of these predictors, significant regression coefficients could be estimated separately for these effects.

11.4.3.4 Charleston Studies. In one of the earliest investigations, Fairey and Gray (1970) conducted a retrospective study of lead poisoning cases in Charleston, South Carolina. Two-inch core soil samples were collected from 170 randomly selected sites in the city and were compared with soil samples taken from homes where 37 cases of lead poisoning had occurred. The soil lead values obtained ranged from 1 to 12,000 μg/g, with 75 percent of the samples containing less than 500 μg/g. A significant relationship between soil lead levels and lead poisoning cases was established; 500 μg/g was used as the cutpoint in the chi-square contingency analysis. Fairey and Gray were the first to examine this complex problem and, although their data support the soil lead hypothesis, the relationship between soil lead and blood lead levels could not be quantified. Furthermore, because no other source of lead was measured, any positive association could have been confounded by additional sources of lead, such as paint or air.

A later study by Galke et al. (1975), in Charleston, used a house-to-house survey to recruit 194 black preschool children. Soil, paint and air lead exposures as measured by traffic density were established for each child. When the population was divided into two groups based on the median soil lead value (585 μg/g), a 5 μg/dl difference in blood lead levels was obtained. Soil lead exposure for this population ranged from 9 to 7890 μg/g. Vehicle traffic patterns were defined by area of recruitment as being high or low. A multiple regression analysis of the data showed that vehicle traffic patterns, lead level in exterior siding

paint, and lead in soil were all independently and significantly related to blood lead levels. Using the model described in Appendix 11B, the following coefficients and standard errors were obtained:

Factor	Coefficient	Asymptotic Standard Error
Intercept (μg/dl)	25.92	1.61
Pica (1 = eater, 0 = otherwise)	7.23	1.60
Traffic Pattern (1 = high, 0 = low)	7.11	1.48
Siding paint (mg/cm^2)	0.33	0.11
Door paint (mg/cm^2)	0.18	0.12
Soil lead (mg/g)	1.46	0.59

Multiple R^2 = 0.386
Residual standard deviation = 0.2148 (geometric standard deviation = 1.24)

11.4.3.5 Barltrop Studies. Barltrop et al. (1974) described two studies in England investigating the soil lead to blood lead relationship. In the first study, children aged 2 and 3 and their mothers from two towns chosen for their soil lead content had their blood lead levels determined from a capillary sample. Hair samples were also collected and analyzed for lead. Lead content of the suspended particulate matter and soil was measured. Soil samples for each home were a composite of several 2-inch core samples taken from the yard of each home. Chemical analysis of the lead content of soil in the two towns showed a 2- to 3-fold difference, with the values in the control town about 200 to 300 μg/g compared with about 700 to 1000 μg/g in the exposed town. A difference was also noted in the mean air lead content of the two towns, 0.60 $\mu g/m^3$ compared with 0.29 $\mu g/m^3$. Although this difference existed, both air lead values were thought low enough not to affect the blood level values differentially. Mean surface soil lead concentrations for the two communities were statistically different, the means for the high and low community being 909 and 398 μg/g, respectively. Despite this difference, no statistically significant differences in maternal blood lead levels or children's blood or hair lead levels were noted. Further statistical analysis of the data, using correlational analysis on either raw or log-transformed blood lead data, likewise failed to show a statistical relationship of soil lead with either blood lead or hair lead.

The second study was reported in both preliminary and final form (Barltrop et al., 1974; Barltrop, 1975). In the more detailed report (Barltrop, 1975), children's homes were classified by their soil lead content into three groups, namely: less than 1,000; 1,000 to 10,000; and greater than 10,000 μg/g. As shown in Table 11-45, children's mean blood lead levels increased correspondingly from 20.7 to 29.0 μg/dl. Mean soil lead levels for the low and high soil exposure groups were 420 and 13,969 μg/g, respectively. Mothers' blood levels,

however, did not reflect this trend; nor were the children's fecal lead levels different across the soil exposure areas.

An analysis of the data in Table 11-45 gives the following model:

blood lead (μg/dl) = 0.64 soil lead (1000 μg/g) + 20.98

No confidence intervals were calculated since the calculations were based on means.

TABLE 11-45. MEAN BLOOD AND SOIL LEAD CONCENTRATIONS IN ENGLISH STUDY

Category of soil lead, μg/g	Sample size	Children's blood lead, μg/dl	Soil lead, μg/g
<1000	29	20.7	420
1000-10000	43	23.8	3390
>10000	10	29.0	13969

Source: Barltrop, 1975.

11.4.3.6 The British Columbia Studies. Neri et al. (1978) studied blood lead levels in children living in Trail, British Columbia. These blood lead measurements were made by the capillary method. An episode of poisoning of horses earlier had been traced to ingestion of lead. Environmental monitoring at that time did not suggest that a human health risk existed. However, it was later thought wise to conduct a study of lead absorption in the area.

Trail had been the site of a smelter since the turn of the century. The smelter had undergone numerous changes for reasons of both health and productivity. At the time of the blood lead study, the smelter was emitting 300 pounds of lead daily, with ambient air lead levels at about 2 $\mu g/m^3$ in 1975. Nelson, BC was chosen as the control city. The cities are reasonably close (~30 miles distant), are similar in population, and served by the same water basin. The average air lead level in Nelson during the study was 0.5 $\mu g/m^3$.

Initial planning called for the sampling of 200 children in each of three age groups (1-3 years, 1st grade and 9th grade) from each of the two sites. A strike at the smelter at the onset of the study caused parts of the Trail population to move. Hence, the recruited sample deviated from the planned one. School children were sampled in May 1975 at their schools while the 1- to 3-year olds were sampled in September 1975 at a clinic or home. This delayed sampling was intentional to allow those children to be exposed to the soil and dust for the entire summer. Blood and hair samples were collected from each child.

Blood samples were analyzed for lead by anodic stripping voltammetry. The children in the younger age groups living in Trail had higher blood lead levels than those living in Nelson. An examination of the frequency distributions of the blood lead levels showed that the entire frequency of the distribution shifted between the residents of the two cities. Interestingly, there was no difference in the ninth grade children.

Table 11-46 displays the results of the soil lead levels along with the blood lead levels obtained in the earlier study. Blood lead levels were higher for 1- to 3-year olds and first graders in the two nearest-to-smelter categories than in the far-from-smelter category. Again, no difference was noted for the ninth graders.

An EPA analysis of the Neri et al. (1978) data gives the following models for children 1- to 3-years old:

Blood lead (μg/dl) = 0.0076 soil lead (μg/g) + 15.43, and

Blood lead (μg/dl) = 0.0046 soil lead (μg/g) + 16.37

for children in grade one. No confidence intervals were calculated since the analysis was based on means.

TABLE 11-46. LEAD CONCENTRATION OF SURFACE SOIL AND CHILDREN'S BLOOD BY RESIDENTIAL AREA OF TRAIL, BRITISH COLUMBIA

Residential area(s)	Mean soil lead concentration (μg/g) ± standard error (and no. of samples)	Blood lead concentration (μg/dl), mean ± standard error (and no. of children)	
		1- to 3-year olds	Grade one children
1 and 2	225 ± 39 (26)	17.2 ± 1.1 (27)	18.0 ± 1.9 (18)
5	777 ± 239 (12)	19.7 ± 1.5 (11)	18.7 ± 2.3 (12)
9	570 ± 143 (11)	20.7 ± 1.6 (19)	19.7 ± 1.0 (16)
3, 4, and 8	1674 ± 183 (53)	27.7 ± 1.8 (14)	23.8 ± 1.3 (31)
6 and 7	1800 ± 212 (51)	30.2 ± 3.0 (16)	25.6 ± 1.5 (26)
Total	1320 ± 212 (153)	22.4 ± 1.0 (87)	21.9 ± 0.7 (103)

Source: Schmitt et al., 1979.

11.4.3.7 Other Studies of Soil and Dusts. Lepow et al. (1975) studied the lead content of air, house dust and dirt, as well as the lead content of dirt on hands, food and water, to determine the cause of chronically elevated blood lead levels in 10 children 2- to 6-years-old

in Hartford, Connecticut. Lead-based paints had been eliminated as a significant source of lead for these children. Ambient air lead concentrations varied from 1.7 to 7.0 $\mu g/m^3$. The mean lead concentration in dirt was 1,200 µg/g and in dust, 11,000 µg/g. The mean concentration of lead in dirt on children's hands was 2,400 µg/g. The mean weight of samples of dirt from hands was 11 mg, which represented only a small fraction of the total dirt on hands. Observation of the mouthing behavior in these young children led to the conclusion that the hands-in-mouth exposure route was the principal cause of excessive lead accumulation.

Several studies have investigated the mechanism by which lead from soil and dust gets into the body (Sayre et al., 1974; Ter Haar and Aronow, 1974). Sayre et al. (1974) in Rochester, New York, demonstrated the feasibility of house dust as a source of lead for children. Two groups of houses, one inner city and the other suburban, were chosen for the study. Lead-free sanitary paper towels were used to collect dust samples from house surfaces and the hands of children (Vostal et al., 1974). The medians for the hand and household samples were used as the cutpoints in the chi-square contingency analysis. A statistically significant difference between the urban and suburban homes for dust levels was noted, as was a relationship between household dust levels and hand dust levels (Lepow et al., 1975).

Ter Haar and Aronow (1974) investigated lead absorption in children that can be attributed to ingestion of dust and dirt. They reasoned that because the proportion of the naturally occurring isotope of ^{210}Pb varies for paint chips, airborne particulates, fallout dust, house dust, yard dirt and street dirt, it would be possible to identify the sources of ingested lead. They collected 24-hour excreta from eight hospitalized children on the first day of hospitalization. These children, 1- to 3-years old, were suspected of having elevated body burdens of lead, and one criterion for the suspicion was a history of pica. Ten children of the same age level, who lived in good housing in Detroit and the suburbs, were selected as controls and 24-hour excreta were collected from them. The excreta were dried and stable lead as well as ^{210}Pb content determined. For seven hospitalized children, the stable lead mean value was 22.43 µg/g dry excreta, and the eighth child had a value of 1640 µg/g. The controls' mean for stable lead was 4.1 µg/g dry excreta. However, the respective means for ^{210}Pb expressed as pCi/g dry matter were 0.044 and 0.040. The authors concluded that because there is no significant difference between these means for ^{210}Pb, the hypothesis that young children with pica eat dust is not supported. The authors further concluded that children with evidence of high lead intake did not have dust and air suspended particulate as the sources of their lead. It is clear that air suspended particulate did not account for the lead levels in the hospitalized children. However, the ^{210}Pb concentrations in dust and feces were similar for all children, making it difficult to estimate the dust contribution.

Heyworth et al. (1981) studied a population of children exposed to lead in mine tailings. These tailings were used in foundations and playgrounds, and had a lead content ranging from

10,000 to 15,000 µg/g. In December 1979 venous blood samples and hair were collected from 181 of 346 children attending two schools in Western Australia. One of the schools was a primary school; the other was a combined primary and secondary school. Parents completed questionnaires covering background information as well as information regarding the children's exposure to the tailings. Blood lead levels were determined by the AAS method of Farrely and Pybos. Good quality control measures were undertaken for the study, especially for the blood lead levels. Blood lead levels were higher in boys vs. girls (mean values were 14.0 and 10.4 µg/dl, respectively). This difference was statistically significant. Five percent of the children (n = 9) had blood lead levels greater than 25 µg/dl. Five of the children had blood lead levels greater than 30 µg/dl. Blood lead levels decreased significantly with age and were slightly lower in children living on properties on which tailings were used. However, they were higher for children attending the school that used the tailings in the playground.

Landrigan et al. (1982) studied the impact on soil and dust lead levels on removal of leaded paint from the Mystic River Bridge in Masschusetts. Environmental studies in 1977 indicated that surface soil directly beneath the bridge had a lead content ranging from 1300 to 1800 µg/g. Analysis of concomitant trace elements showed that the lead came from the bridge. A concurrent survey of children living in Chelsea (vicinity of bridge) found that 49 percent of 109 children had blood lead levels greater than or equal to 30 µg/dl. Of children living more distant from the bridge "only" 37 percent had that level of blood lead.

These findings prompted the Massachusetts Port Authority to undertake a program to delead the bridge. Paint on parts of the bridge that extended over neighborhoods was removed by abrasive blasting and replaced by zinc primer. Some care was undertaken to minimize both the occupational as well as environmental exposures to lead as a result of the blasting process.

Concurrently with the actual deleading work, a program of air monitoring was established to check on the environmental lead exposures being created. In June 1980 four air samples taken at a point 27 meters from the bridge had a mean lead content of 5.32 $\mu g/m^3$. As a result of these findings air pollution controls were tightened; mean air lead concentrations 12 meters from the bridge in July were 1.43 $\mu g/m^3$.

Samples of the top 1 cm of soil were obtained in July 1980 from within 30, 30 to 80, and 100 meters from the bridge. Comparison samples from outside the area were also obtained. Samples taken directly under the bridge had a mean lead content of 8127 µg/g. Within 30 meters of the bridge, the mean content was 3272 µg/g, dropping to 457 µg/g at 30 to 80 meters. At 100 meters the soil lead level dropped to 197 µg/g. Comparison samples ranged from 83 to 165 µg/g depending on location.

Fingerstick blood samples were obtained on 123 children 1-5 years of age living within 0.3 km of the bridge in Charlestown. Four children (3.3 percent) had blood lead levels

greater than 30 µg/dl with a maximum of 35 µg/dl. All four children lived within two blocks of the bridge. Two of the four had lead paint in their homes but it was intact. None of the 76 children living more than two blocks from the bridge had blood leads greater than or equal to 30 µg/dl, a statistically significant difference.

Shellshear's (1973) case report from New Zealand ascribes a medically diagnosed case of lead poisoning to high soil lead content in the child's home environment. Shellshear et al. (1975) followed up his case report of increased lead absorption resulting from exposure to lead contaminated soil with a study carried out in Christchurch, New Zealand. Two related activities comprised the study. First, from May 1973 to November 1973, a random study of pediatric admissions to a local hospital was made. Blood samples were taken and analyzed for lead. Homes were visited and soil samples were collected and analyzed for lead. Lead analyses for both soil and blood were conducted by AAS. Second, a soil survey of the area was undertaken. Whenever a soil lead value greater than 300 µg/g was found and a child aged one to five was present, the child was referred for blood testing.

The two methods of subject recruitment yielded a total of 170 subjects. Eight (4.7 percent) of the children had blood lead equal to or greater than 40 µg/dl, and three of them had a blood lead equal to or greater than 80 µg/dl. No correlation with age was noted. The mean blood lead of the pediatric admissions was 17.5 µg/dl with an extremely large range (4 to 170 µg/dl). The mean blood lead for soil survey children was 19.5 µg/dl.

Christchurch was divided into two sections based on the date of development of the area. The inner area had developed earlier and a higher level of lead was used there in the house paints. The frequency distribution of soil lead levels showed that the inner zone samples had much higher soil lead levels than the outer zone. Furthermore, analysis of the soil lead levels by type of exterior surface of the residential unit showed that painted exteriors had higher soil lead values than brick, stone or concrete block exteriors.

Analysis of the relationship between soil lead and blood lead was restricted to children from the sampled hospital who had lived at their current address for at least 1 year. Table 11-47 presents the analysis of these results. Although the results were not statistically significant, they are suggestive of an association.

Analysis of the possible effect of pica on blood lead levels showed the mean blood lead for children with pica to be 32 µg/dl while those without pica had a mean of 16.8 µg/dl. The pica blood lead mean was statistically significantly higher than the non-pica mean.

Wedeen et al. (1978) reported a case of lead nephropathy in a black female who exhibited geophagia. The patient, who had undergone chelation therapy, eventually reported that she had a habit of eating soil from her garden in East Orange, New Jersey. During spring and summer, she continuously kept soil from her garden in her mouth while gardening. She even put a supply away for winter. The soil was analyzed for lead and was found to contain almost 700 µg/g.

TABLE 11-47. ANALYSIS OF RELATIONSHIP BETWEEN SOIL LEAD AND BLOOD LEAD IN CHILDREN

Area of city	Soil lead (µg/g) Mean	Range	n	Blood lead µg/dl) Mean	Range
Inner zone	1950	30-11000	21	25.4	4-170
Outer zone	150	30-1100	47	18.3	5-84

Source: Shellshear (1973).

The authors estimated that the patient consumed 100 to 500 mg of lead each year. One month after initial hospitalization her blood lead level was 70 µg/dl.

11.4.3.8 Summary of Soil and Dust Lead. Studies relating soil lead to blood lead levels are difficult to compare. The relationship obviously depends on depth of soil lead, age of the children, sampling method, cleanliness of the home, mouthing activities of the children, and possibly many other factors. Table 11-48 gives some estimated slopes taken from several different studies. The range of these values is quite large, ranging from 0.6 to 7.6. The values from the Stark et al. (1980) study of about 2 µg/dl per mg/g represent a reasonable median estimate.

The relationship of house dust lead to blood lead is even more difficult to obtain. Table 11-49 contains some values for three studies that give data permitting such caculations. The median value of 1.8 µg/dl per mg/g for 2-3 years old in the Stark study may also represent a reasonable value for use here.

TABLE 11-48. ESTIMATES OF THE CONTRIBUTION OF SOIL LEAD TO BLOOD LEAD

Study	Range of soil lead values (μg/g)	Depth of sample	Estimated slope ($X10^3$)	Sample size	R^2
Angle and McIntire (1982) study of children in Omaha, NE	16 to 4792	2"	6.8	1075	.198
Stark et al. (1982) study of children New Haven, CT	30 to 7000 (age 0-1)	½"	2.2	153	.289
	30 to 7600 (age 2-3)		2.0	334	.300
Yankel et al. (1977) study of children in Kellogg, ID	50 to 24,600	3/4"	1.1	860	.662
Galke et al. (1975) study of chilren in Charleston, SC	9 to 7890	2"	1.5	194	.386
Barltrop et al. (1975) study of children in England	420 to 13,969 (group means)	2"	0.6	82	NA*
Neri et al. (1978) study of children in British Columbia	225-1800 (group means, age 1-3)	NA	7.6	87	NA
	225-1800 (group means, age 2-3)	NA	4.6	103	NA

*NA means Not Available.

TABLE 11-49. ESTIMATES OF THE CONTRIBUTION OF HOUSEDUST TO BLOOD LEAD IN CHILDREN

Study	Range of dust Lead values (μg/g)	Age range in years	Estimated slope ($X10^3$)	Sample Size	R^2
Angle and McIntire (1979) study in Omaha, NE	18-5571	1-18	7.18	1074	.198
		6-18	3.36	832	.262
Stark et al. (1982) study in New Haven, CT	70-7600	0-1	4.02	153	.289
	40-7600	2-3	1.82	334	.300
	9-4900	4-7	0.02	439	.143
Yankel et al. (1977) study in Kellogg, ID	50-35,600	0-4	0.19	185	.721
		5-9	0.20	246	.623

11.4.4 Paint Lead Exposures

A major source of environmental lead exposure for the general population comes from lead contained in both interior and exterior paint on dwellings. The amount of lead present, as well as its accessibility, depends upon the age of the residence (because older buildings contain paint manufactured before lead content was regulated) and the physical condition of the paint. It is generally accepted by the public and by health professionals that lead-based paint is one major source of overtly symptomatic pediatric lead poisoning in the United States (Lin-Fu, 1973).

The level and distribution of lead paint in a dwelling is a complex function of history, geography, economics, and the decorating habits of its residents. Lead pigments were the first pigments produced on a large commercial scale when the paint industry began its growth in the early 1900's. In the 1930's lead pigments were gradually replaced with zinc and other opacifiers. By the 1940's, titanium dioxide became available and is now the most commonly used pigment for residential coatings. There was no regulation of the use of lead in house paints until 1955, when the paint industry adopted a voluntary standard that limited the lead content in interior paint to no more than 1 percent by weight of the nonvolatile solids. At about the same time, local jurisdictions began adopting codes and regulations that prohibited the sale and use of interior paints containing more than 1 percent lead (Berger, 1973a,b).

In spite of the change in paint technology and local regulations governing its use, and contrary to popular belief, interior paint with significant amounts of lead was still available in the 1970's. Studies by the National Bureau of Standards (1973) and by the U.S.

Consumer Product Safety Commission (1974) showed a continuing decrease in the number of interior paints with lead levels greater than 1 percent. By 1974, only 2 percent of the interior paints sampled were found to have greater than 1 percent lead in the dried film (U.S. Consumer Product Safety Commission, 1974).

The level of lead in paint in a residence that should be considered hazardous remains in question. Not only is the total amount of lead in paint important, but also the accessibility of the painted surface to a child, as well as the frequency of ingestion must be considered. Attempts to set an acceptable lead level, in situ, have been unsuccessful, and preventive control measures of lead paint hazards has been concerned with lead levels in currently manufactured paint. In one of its reviews, the NAS concluded: "Since control of the lead paint hazard is difficult to accomplish once multiple layers have been applied in homes over two to three decades, and since control is more easily regulated at the time of manufacture, we recommend that the lead content of paints be set and enforced at time of manufacture" (National Academy of Sciences, 1976).

Legal control of lead paint hazards is being attempted by local communities through health or housing codes and regulations. At the Federal level, the Department of Housing and Urban Development has issued regulations for lead hazard abatement in housing units assisted or supported by its programs. Generally, the lead level considered hazardous ranges from 0.5 to 2.5 mg/cm^2, but the level of lead content selected appears to depend more on the sensitivity of field measurement (using X-ray fluorescent lead detectors) than on direct biological dose-response relationships. Regulations also require lead hazard abatement when the paint is loose, flaking, peeling or broken, or in some cases when it is on surfaces within reach of a child's mouth.

Some studies have been carried out to determine the distribution of lead levels in paint in residences. A survey of lead levels in 2370 randomly selected dwellings in Pittsburgh provides some indication of the lead levels to be found (Shier and Hall, 1977). Figure 11-22 shows the distribution curves for the highest lead level found in dwellings for three age groupings. The curves bear out the statement often made that paint with high levels of lead is most frequently found in pre-1940 residences. One cannot assume, however, that high lead paint is absent in dwellings built after 1940. In the case of the houses surveyed in Pittsburgh, about 20 percent of the residences built after 1960 have at least one surface with more than 1.5 mg/cm^2.

The distribution of lead within an individual dwelling varies considerably. Lead paint is most frequently found on doors and windows where lead levels greater than 1.5 mg/cm^2 were found on 2 percent of the surfaces surveyed, whereas only about 1 percent of the walls had lead levels greater than 1.5 mg/cm^2 (Shier and Hall, 1977).

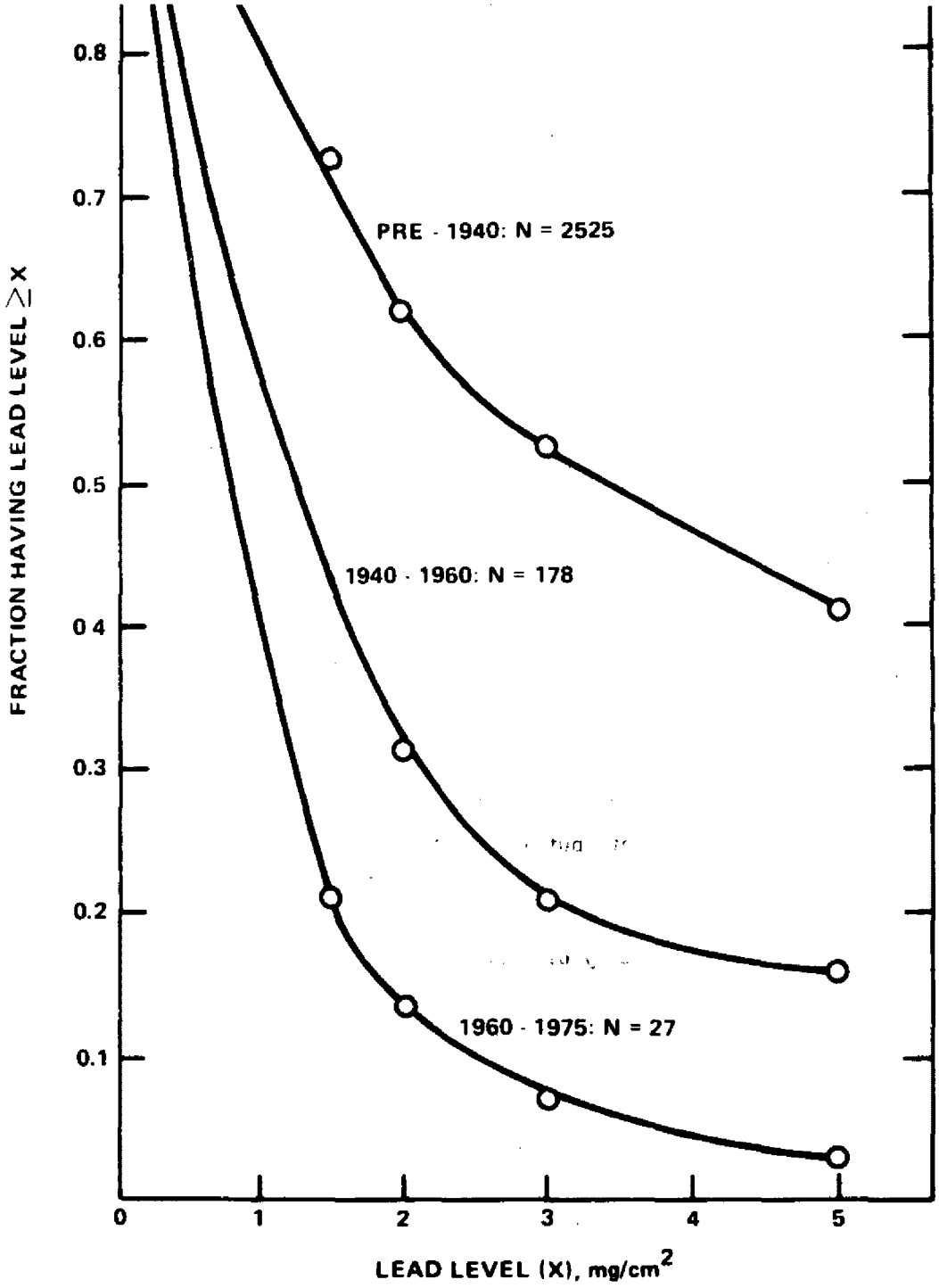

Figure 11-22. Cumulative distribution of lead levels in dwelling units.

In a review of the literature (Lin-Fu, 1973) found general acceptance that the presence of lead in paint is necessary but not sufficient evidence of a hazard. Accessibility in terms of peeling, flaking or loose paint also provide evidence for the presence of a hazard. Of the total samples surveyed, about 14 percent of the residences had accessible paint with a lead content greater than 1.5 mg/cm^2. As discussed in Section 7.3.2.1.2, one must note that lead oxides of painted surfaces contribute to the lead level of house dust.

It is not possible to extrapolate the results of the Pittsburgh survey nationally; however, additional data from a pilot study of 115 residences in Washington, DC, showed similar results (Hall 1974).

An attempt was made in the Pittsburgh study to obtain information about the correlation between the quantity and condition of lead paint in buildings, and the blood lead of children who resided there (Urban, 1976). Blood lead analyses and socioeconomic data for 456 children were obtained, along with the information about lead levels in the dwelling. Figure 11-23 is a plot of the blood lead levels vs. the fraction of surfaces within a dwelling with lead levels of at least 2 mg/cm^2. Analysis of the data shows a low correlation between the blood lead levels of the children and fraction of surfaces with lead levels above 2 mg/cm^2, but there is a stronger correlation between the blood lead levels and the condition of the painted surfaces in the dwellings in which children reside. This latter correlation appeared to be independent of the lead levels in the dwellings.

Two other studies have attempted to relate blood lead levels and paint lead as determined by X-ray fluorescence. Reece et al. (1972) studied 81 children from two lower socioeconomic communities in Cincinnati. Blood leads were analyzed by the dithizone method. There was considerable lead in the home environment, but it was not reflected in the children's blood lead. Analytical procedures used to test the hypothesis were not described; neither were the raw data presented.

Galke et al. (1975), in their study of inner city black children measured the paint lead, both interior and exterior, as well as soil and traffic exposure. In a multiple regression analysis, exterior siding paint lead was found to be significantly related to blood lead levels.

Evidence indicates that a source of exposure in childhood lead poisoning is peeling lead paint and broken lead-impregnated plaster found in poorly maintained houses. There are also reports of exposure cases that cannot be equated with the presence of lead paint. Further, the analysis of paint in homes of children with lead poisoning has not consistently revealed a hazardous lead content (Lin-Fu, 1973). For example, one paper reported 5466 samples of paint obtained from the home environment of lead poisoning cases in Philadelphia between 1964 and 1968. Among these samples of paint, 67 percent yielded positive findings, i.e., paint with more than 1 percent lead (Tyler, 1970).

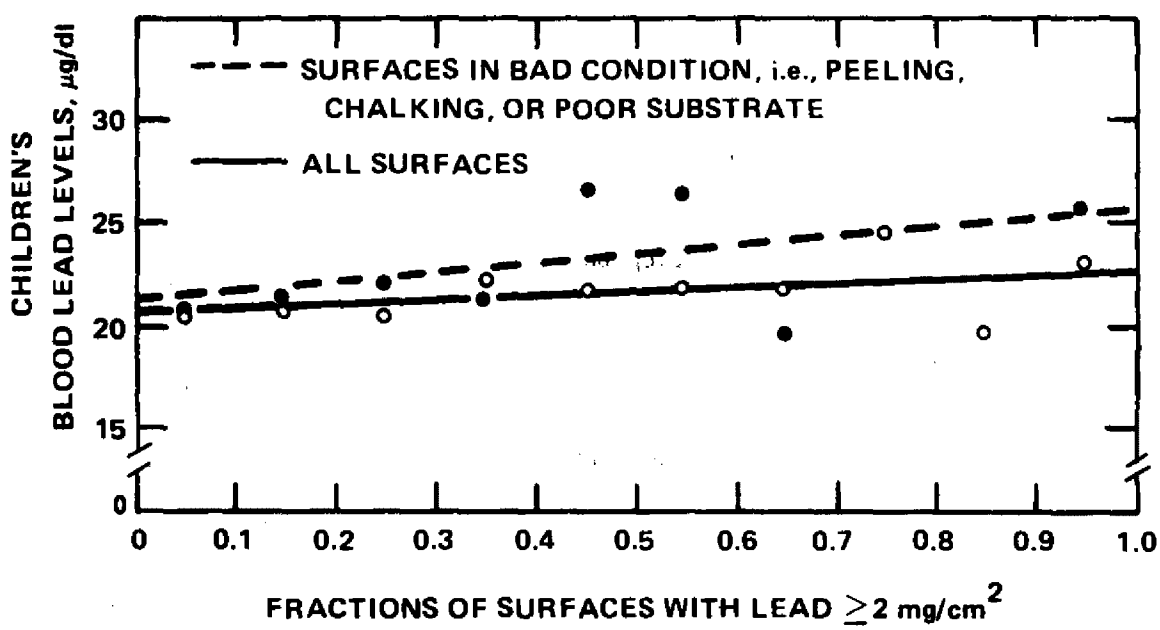

Figure 11-23. Correlation of children's blood lead levels with fractions of surfaces within a dwelling having lead concentrations ≥ 2 mg Pb/cm².

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Data published or made available by the Centers for Disease Control also show that a significant number of children with undue lead absorption occupy buildings that were inspected for lead-based paint hazards, but in which no hazard could be demonstrated (U.S. Centers for Disease Control, 1977a; Hopkins and Houk, 1976). Table 11-50 summarizes the data obtained from the HEW funded lead-based paint poisoning control projects for Fiscal Years 1981, 1979, 1978, 1975, and 1974. These data show that in Fiscal Years 1974, 1975, and 1978, about 40 to 50 percent of confirmed cases of elevated blood lead levels, a possible source of lead paint hazard could not be located. In fiscal year 1981, the U.S. Centers for Disease Control (1982a,b), screened 535,730 children and found 21,897 with lead toxicity. Of these, 15,472 dwellings were inspected and 10,666 or approximately 67 percent were found to have leaded paint. The implications of these findings are not clear. The findings are presented in order to place in proper perspective both the concept of total lead exposure and the concept that lead paint is one source of lead that contributes to the total body load. The background contribution of lead from other sources is still not known, even for those children for whom a potential lead paint hazard has been identified; nor is it known what proportion of lead came from which source.

TABLE 11-50. RESULTS OF SCREENING AND HOUSING INSPECTION IN CHILDHOOD LEAD POISONING CONTROL PROJECT BY FISCAL YEAR

Results	Fiscal Year				
	1981	1979	1978	1975	1974
Children screened	535,730	464,751	397,963	440,650	371,955
Children with elevated lead exposure	21,897	32,537	25,801	28,597[a]	16,228[a]
Dwellings inspected	15,472	17,911	36,138	30,227	23,096
Dwellings with lead hazard	10,666	12,461	18,536	17,609	13,742

[a]Confirmed blood lead level $\geq$40 µg/dl.

Source: U.S. Centers for Disease Control (1977a, 1979, 1980, 1982a,b); Hopkins and Houk, 1976.

11.5 SPECIFIC SOURCE STUDIES

The studies reviewed in this section all provide important information regarding specific environmental sources of airborne lead that play a significant role in population blood lead levels. These studies also illustrate several interesting approaches to this issue.

11.5.1 Combustion of Gasoline Antiknock Compounds

11.5.1.1 Isotope Studies. Two field investigations have attempted to derive estimates of the amount of lead from gasoline that is absorbed by the blood of individuals. Both of these investigations used the fact that non-radioactive isotopes of lead are stable. The varying proportions of the isotopes present in blood and environmental samples can indicate the source of the lead. The Isotopic Lead Experiment (ILE) is an extensive study that attempted to use differing proportions of the isotopes in geologic formations to infer the proportion of lead in gasoline that is absorbed by the body. The other study utilized existing natural shifts in isotopic proportions in an attempt to do the same thing.

11.5.1.1.1 Italy. The ILE is a large scale community study in which the geologic source of lead for antiknock compounds in gasoline was manipulated to change the isotopic composition of the atmosphere (Garibaldi et al., 1975; Facchetti, 1979). Preliminary investigation of the environment of Northwest Italy, and the blood of residents there, indicated that the ratio of lead 206/207 in blood was a constant, about 1.16, and the ratio in gasoline was about 1.18. This preliminary study also suggested that it would be possible to substitute for the currently used geologic sources of lead for antiknock production, a geologically distinct source of lead from Australia that had an isotopic 206/207 ratio of 1.04. It was hypothesized that the resulting change in blood lead 206/207 ratios (from 1.16 to a lower value) would indicate the proportion of lead in the blood of exposed human populations attributable to lead in the air contributed by gasoline combustion in the study area.

Baseline sampling of both the environment and residents in the geographic area of the study was conducted in 1974-75. The sampling included air, soil, plants, lead stock, gasoline supplies, etc. Human blood sampling was done on a variety of populations within the area. Both environmental and human samples were analyzed for lead concentrations as well as isotopic 206/207 composition.

In August 1975 the first switched (Australian lead labelled) gasoline was introduced; although it was originally intended to get a 100 percent substitution, practical and logistical problems resulted in only a 50 percent substitution being achieved by this time. By May 1977, these problems were worked out and the substitution was practically complete. The substitution was maintained until the end of 1979, when a partial return to use of the original sources of lead began. Therefore, the project had four phases: phase zero - background; phase one - partial switch; phase two - total switch; and phase three - switchback.

Airborne lead measurements were collected in a number of sites to generate estimates of the lead exposure that was experienced by residents of the area. Turin, the major city of the region, was found to have a much greater level of atmospheric lead than the surrounding countryside. There also appeared to be fairly wide seasonal fluctuations.

The isotopic lead ratios obtained in the samples analyzed are displayed in Figure 11-24. It can easily be seen that the airborne particulate lead rapidly changed its isotope ratio in line with expectations. Changes in the isotope ratios of the blood samples appeared to lag somewhat behind. Background blood lead ratios for adults were 1.1591 ± 0.0043 in rural areas and 1.1627 ± 0.0022 in Turin in 1975. For Turin adults, a mean isotopic ratio of 1.1325 was obtained in 1979, clearly less than background. Isotopic ratios for Turin schoolchildren, obtained starting in 1977, tended to be somewhat lower than the ratios for Turin adults.

Preliminary analysis of the isotope ratios in air lead allowed for the estimation of the fractional contribution of gasoline in the city of Turin, in small communities within 25 km of Turin, and in small communities beyond 25 km (Facchetti and Geiss, 1982). At the time of maximal use of Australian lead isotope in gasoline (1978-79), about 87.3 percent of the air lead in Turin and 58.7 percent of the air lead in the countryside was attributable to gasoline. The determination of lead isotope ratios was essentially independent of air lead concentrations. During that time, air lead averaged about 2.0 $\mu g/m^3$ in Turin (from 0.88 to 4.54 $\mu g/m^3$ depending on location of the sampling site), about 0.56 $\mu g/m^3$ in the nearby communities (0.30 to 0.67 $\mu g/m^3$) and about 0.30 $\mu g/m^3$ in more distant (> 25 km) locations.

Blood lead concentrations and isotope ratios for 35 adult subjects were determined on two or more occasions during phases 0-2 of the study (see Appendix C). Their blood lead isotope ratios decreased over time and the fraction of lead in their blood attributable to the Australian lead-labelled gasoline could be estimated independently of blood lead concentration (see Appendix C for estimation method). The mean fraction of blood lead attributable to the Australian lead-labelled gasoline ranged from 23.7 ± 5.4 percent in Turin to 12.5 ± 7.1 percent in the nearby (< 25 km) countryside and 11.0 ± 5.8 percent in the remote countryside. These likely represent minimal estimates of fractions of blood lead derived from gasoline due to: (1) use of some non-Australian lead-labelled gasoline brought into the study area from outside; (2) probable insufficient time to have achieved steady-state blood lead isotope ratios by the time of the switchback; (3) probable insufficient time to fully reflect delayed movement of the Australian lead from gasoline via environmental pathways in addition to air.

These results can be combined with the actual blood lead concentrations to estimate the fraction of gasoline uptake attributable or not attributable to direct inhalation. The results are shown in Table 11-51 (based on a suggestion by Dr. Facchetti). From Section 11.4.1, we conclude that an assumed value of β=1.6 is plausible for predicting the amount of

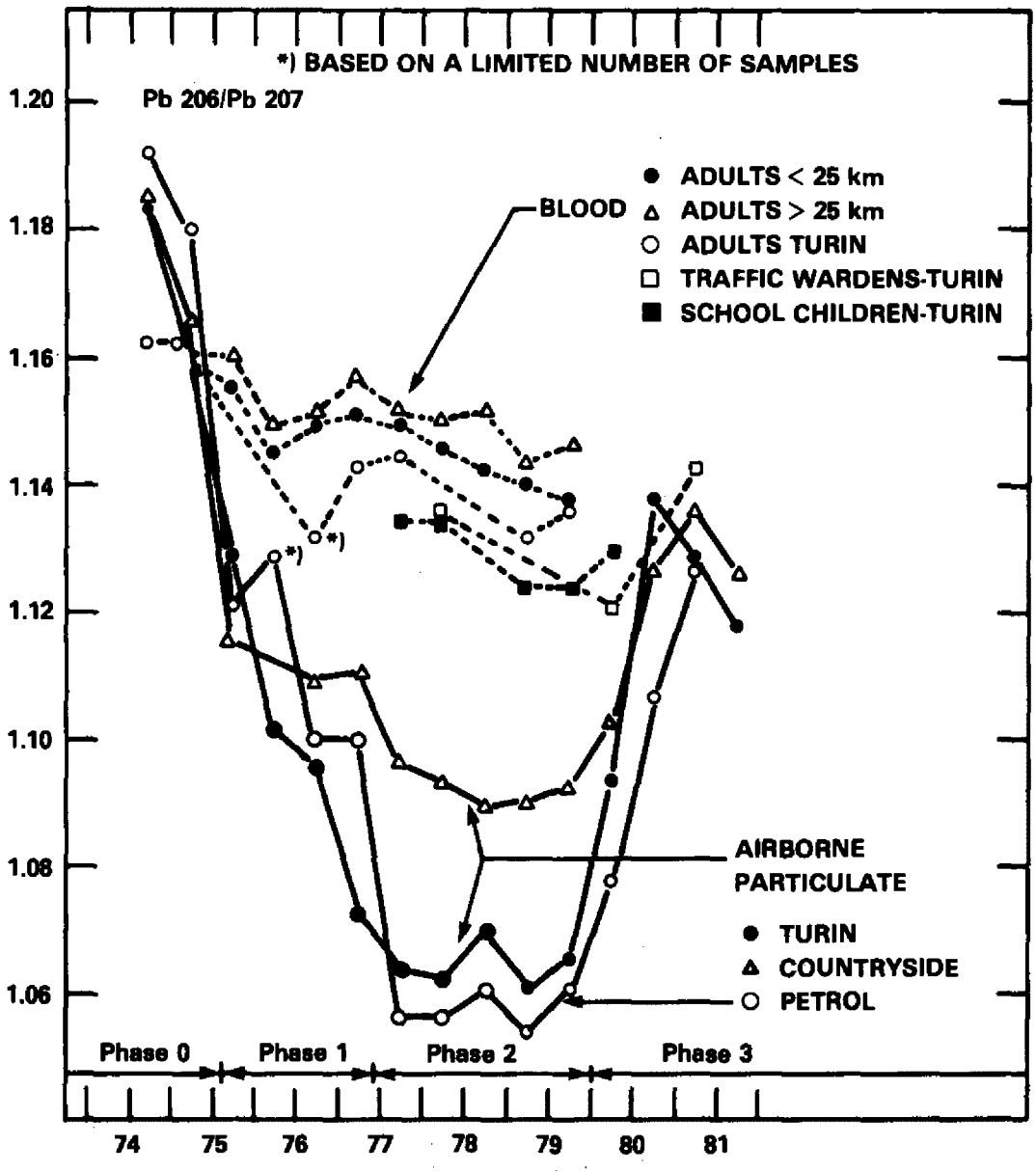

Figure 11-24. Change in Pb-206/Pb-207 ratios in petrol, airborne particulate, and blood from 1974 to 1981.

Source: Facchetti and Geiss (1982).

TABLE 11-51. ESTIMATED CONTRIBUTION OF LEADED GASOLINE TO BLOOD LEAD BY INHALATION AND NON-INHALATION PATHWAYS

	Air Lead Fraction From Gasoline[a]	Mean Air Lead Conc.[b] ($\mu g/m^3$)	Blood Pb Fraction From Gasoline[c]	Mean Blood Lead Conc.[d] ($\mu g/dl$)	Blood PB From Gasoline[e] ($\mu g/dl$)	PB From Gasoline In Air[f] ($\mu g/dl$)	Non-Inhaled Pb From Gasoline[g] ($\mu g/dl$)	Estimated Fraction Gas-Lead Inhalation[h]
Location								
Turin	0.873	2.0	0.237	21.77	5.16	2.79	2.37	0.54
<25 km	0.587	0.56	0.125	25.06	3.13	0.53	2.60	0.17
>25 km	0.587	0.30	0.110	31.78	3.50	0.28	3.22	0.08

(a) Fraction of air lead in Phase 2 attributable to lead in gasoline.

(b) Mean air lead in Phase 2, $\mu g/m^3$.

(c) Mean fraction of blood lead in Phase 2 attributable to lead in gasoline.

(d) Mean blood lead concentration in Phase 2, $\mu g/dl$.

(e) Estimated blood lead from gasoline = (c) x (d)

(f) Estimated blood lead from gas inhalation = β x (a) x (b), $\beta = 1.6$.

(g) Estimated blood lead from gas, non-inhalation = (f)-(e)

(h) Fraction of blood lead uptake from gasoline attributable to direct inhalation = (f)/(e)

Data: Facchetti and Geiss (1982), pp. 52-56.

lead absorbed into blood at air lead concentrations less than 2.0 $\mu g/m^3$. The predicted values for lead from gasoline in air (in the ILE) range from 0.28 to 2.79 $\mu g/dl$ in blood due to direct inhalation. The total contribution of blood lead from gasoline is much larger, from 3.50 to 5.16 $\mu g/dl$, suggesting that the non-inhalation contribution of gasoline increases from 2.37 $\mu g/dl$ in Turin to 2.60 $\mu g/dl$ in the near region and 3.22 $\mu g/dl$ in the more distant region. The non-inhalation sources include ingestion of dust and soil lead, and lead in food and drinking water. Efforts are being made to quantify the magnitude of these sources. The average direct inhalation of lead in the air from gasoline is 8 to 17 percent of the total intake attributable to gasoline in the countryside and an estimated 68 percent in the city of Turin. Note that in this sample, the blood lead concentrations are least in the city and highest in the more remote areas. This is not obviously attributable to sex because the city sample was all male. A more detailed statistical investigation is needed.

Lead uptake may also be associated with occupation, sex, age, smoking and drinking habits. The linear exposure model used in Section 11.4 was also used here to estimate the fraction of labelled blood lead from gasoline attributable to exposure via direct inhalation and other pathways. EPA used blood lead measurements in Phase 2 for the 35 subjects for whom repeated measurements allowed estimation of the change in isotope ratios in the blood. Their blood lead concentrations in Phase 2 were also determined, allowing for estimation of the total gasoline contribution to blood lead. Possible covariates included sex, age, cigarette smoking, drinking alcoholic beverages, occupation, residence location and work location. In order to obtain some crude comparisons with the inhalation exposure studies of Section 11.4.1, EPA analysis assigned the air lead values listed in Table 11-52 to various locations. Lower values for air lead in Turin would increase the estimated blood lead inhalation slope above the estimated value 1.70. Since the fraction of time subjects were exposed to workplace air was not known, this was also estimated from the data as about 41 percent (i.e., 9.8 hours/day). The results are shown in Figure 11-25 and Table 11-53. Of all the available variables, only location, sex and inhaled air lead from gasoline proved statistically significant in predicting blood lead attributable to gasoline. The model predictability is fairly good, $R^2 = 0.654$. It should be noted that a certain amount of confounding of variables was unavoidable in this small set of preliminary data, e.g., no female subjects in Turin or in occupations of traffic wardens, etc. There was a systematic increase in estimated non-inhalation contribution from gasoline increase for remote areas, but the cause is unknown. Nevertheless, the estimated non-inhalation contribution of gasoline to blood lead in the ILE study is significant (i.e. 1.8 to 3.4 μg/dl).

TABLE 11-52. ASSUMED AIR LEAD CONCENTRATIONS FOR MODEL

Residence or workplace code	1-4	5	6
Location	outside Turin	Turin residential	Turin central
Air lead concentration	(a)	1.0 $\mu g/m^3$(b)	2.5 $\mu g/m^3$(c)

(a) Use value for community air lead, 0.16 to 0.67 $\mu g/m^3$.

(b) Intermediate between average traffic areas (1.71 g/m^3) and low traffic areas (0.88 g/m^3) in Turin.

(c) Intermediate between average traffic areas (1.71 $\mu g/m^3$) and heavy traffic areas (4.54 g/m^3) in Turin.

The preliminary linear analysis of the overall ILE data set (2161 observations) found that total blood lead levels depended on other covariates for which there were plausible mechanisms of lead exposure, including location, smoking, alcoholic beverages, age and occupation (Facchetti and Geiss 1982). The difference between total blood lead uptake and blood

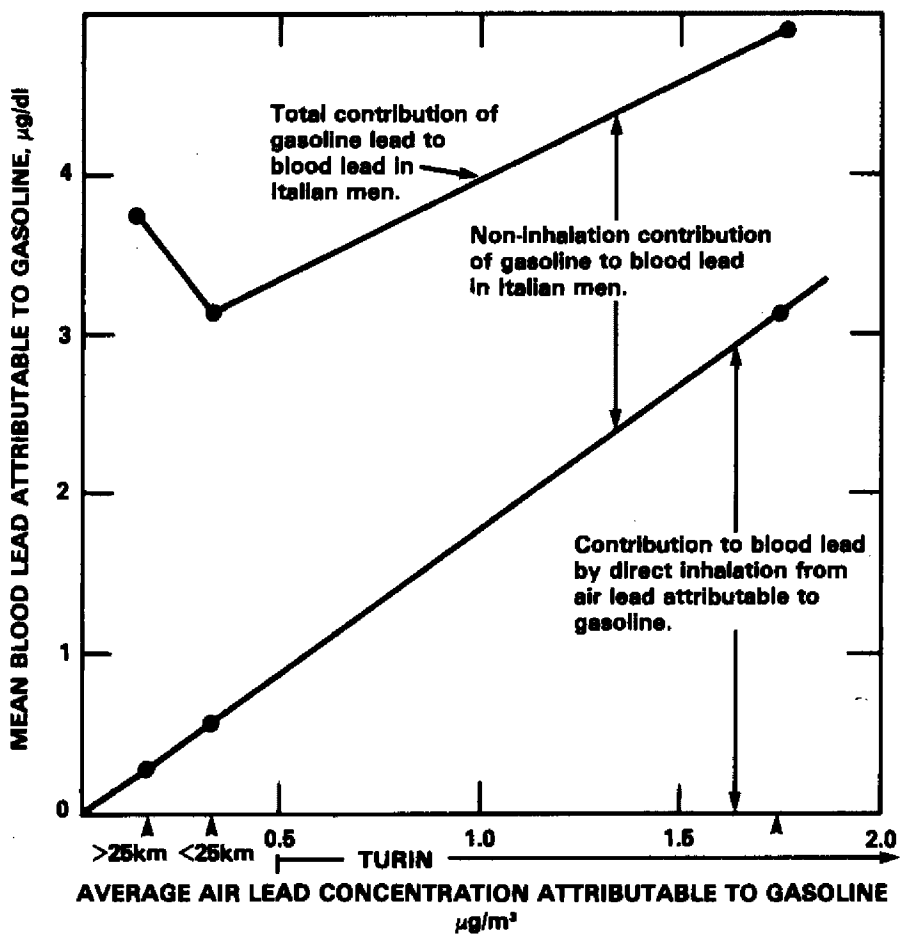

Figure 11-25. Estimated direct and indirect contributions of lead in gasoline to blood lead in Italian men, based on EPA analysis of ILE data (Table 11-53).

lead uptake attributable to gasoline lead has yet to be analyzed in detail, but these analyses suggest that certain important differences may be found. Some reservations have been expressed about the ILE study, both by the authors themselves and by Elwood (1983). These include unusual conditions of meteorology and traffic in Turin, and demographic characteristics of the 35 subjects measured repeatedly that may restrict the generalizability of the study. However, it is clear that changes in air lead attributable to gasoline were tracked by changes in blood

TABLE 11-53. REGRESSION MODEL FOR BLOOD LEAD ATTRIBUTABLE TO GASOLINE

Variable	Coefficient ± Standard Error
Air lead from gas	1.70 ± 1.04 μg/dl per $\mu g/m^3$
LOCATION	
Turin	1.82 ± 2.01 μg/dl
<25 km	2.56 ± 0.59 μg/dl
>25 km	3.42 ± 0.85 μg/dl
Sex	-2.03 ± 0.48 μg/dl for women

lead in Turin residents. The airborne particulate lead isotope ratio quickly achieved new equilibrium levels as the gasoline isotope ratio was changed, and maintained that level during the 2½ years of Phase 2. The blood lead isotope ratios fell slowly during the changeover period, and rose again afterwards as shown in Figure 11-24. Equilibrium was not clearly achieved for blood lead isotope ratios, possibly due to large endogenous pools of old lead stored in the skeleton and slowly mobilized over time. Even with such reservations, this study provides a useful basis for relating blood lead and air lead derived from gasoline combustion.

11.5.1.1.2 United States. Manton (1977) conducted a long term study of 10 subjects whose blood lead isotopic composition was monitored for comparison with the isotopic composition of the air they breathed. Manton had observed that the ratio of $^{206}Pb/^{204}Pb$ in the air varied with seasons in Dallas, Texas; therefore, the ratio of those isotopes should vary in the blood. By comparing the observed variability, estimates could then be made of the amount of lead in air that is absorbed by the blood.

Manton took monthly blood samples from all 10 subjects from April 1974 until June 1975. The blood samples were analyzed for both total lead and isotopic composition. The recruited volunteers included a mix of males and females, and persons highly and moderately exposed to lead. However, none of the subjects was thought to be exposed to more than 1 $\mu g/m^3$ of lead in air. Lead in air samples was collected by Hi-Vol samplers primarily from one site in Dallas. That site, however, had been shown earlier to vary in isotopic composition paralleling another site some 16 miles away. All analyses were carried out under clean conditions with care and caution being exercised to avoid lead contamination.

The isotope ratio of lead $^{206}Pb/^{204}Pb$ increased linearly with time from about 18.45 to 19.35, approximately a 6 percent increase. At least one of the two isotopic lead ratios increased linearly in 4 of the 10 subjects. In one other, they increased but erratically. In

the remainder of the subjects, the isotopic ratios followed smooth curves showing inflection points. The curves obtained for the two subjects born in South Africa were 6 months out of phase with the curves of the native-born Americans. The fact that the isotope ratios in 9 of the 10 subjects varied regularly was thought to indicate that the non-airborne sources of lead varied in isotopic composition very slowly.

The blood lead levels exhibited a variety of patterns, although none of the subjects showed more than a 25 percent change from initial levels. This suggests a reasonably steady state external environment.

Manton carried his analyses further to estimate the percentage of lead in blood that comes from air. He estimated that the percentage varied from 7 to 41 percent, assuming that dietary sources of lead had a constant isotopic ratio while air varied. He calculated the percent contribution according to the following equation:

$$\frac{q}{100+q} = \frac{b}{a}, \quad \text{where}$$

b = rate of change of an isotope ratio in blood,

a = rate of change of the same ratio in the air,

q = constant - the number of atoms of the isotope in the denominator of the airborne lead ratio mixed with 100 atoms of the same isotope of lead from non-airborne sources.

The results are shown in Table 11-54. Slopes were obtained by least squares regression. Percentages of airborne lead in blood varied between 7±3 and 41±3.

TABLE 11-54. RATE OF CHANGE OF $^{206}Pb/^{204}Pb$ AND $^{206}Pb/^{207}Pb$ IN AIR AND BLOOD, AND PERCENTAGE OF AIRBORNE LEAD IN BLOOD OF SUBJECTS 1, 3, 5, 6 AND 9

Subject	Rate of Change per Day		Percentage of Airborne Lead in Blood	
	$^{206}Pb/^{204}Pb$ X 10^{-4}	$^{206}Pb/^{207}Pb$ X 10^{-5}	From $^{206}Pb/^{204}Pb$	From $^{206}Pb/^{207}Pb$
(Air)	17.60 ± 0.77	9.97 ± 0.42	. . .	. . .
1	. . .	0.70 ± 0.30	. . .	7 ± 3
3	5.52 ± 0.55	. . .	31.4 ± 3.4	. . .
5	. . .	3.13 ± 0.34	. . .	31.4 ± 3.7
6	6.53 ± 0.49	4.10 ± 0.25	37.1 ± 2.8	41.1 ± 3.0
9*	3.25	2.01	18.5	20.0

Note: Errors quoted are one standard deviation
*From slope of tangent drawn to the minima of subject's blood curves. Errors cannot realistically be assigned.

Stephens (1981) has extended the analysis of data in Manton's study (Table 11-55). He used the observed air lead concentrations based on actual 24-hour air lead exposures in three adults. He assumed values for breathing rate, lung deposition and absorption into blood to estimate the blood lead uptake attributable to ^{204}Pb by the direct inhalation pathway. Subjects 5, 6 and 9 absorbed far more air lead in fact than was calculated using the values in Table 11-54. The total air lead contribution was 8.4, 4.4 and 7.9 times larger than the direct inhalation. These estimates are sensitive to the assumed parameter values.

In summary, the direct inhalation pathway accounts for only a fraction of the total air lead contribution to blood, the direct inhalation contribution being on the order of 12 to 23 percent of the total uptake of lead attributable to gasoline, using Stephen's assumptions. This is consistent with estimates (i.e. 8 to 54 percent) from the ILE study, taking into account the much higher air lead levels in Turin.

11.5.1.2 Studies of Childhood Blood Lead Poisoning Control Programs. Billick et al. (1979) presented several possible explanations for the observed decline in blood lead levels in New York City children as well as evidence supporting and refuting each. The suggested contributing factors include the active educational and screening program of the New York City Bureau of Lead Poisoning Control, and the decrease in the amount of lead-based paint exposure as a result of rehabilitation or removal of older housing or changes in environmental lead exposure.

Information was only available to partially evaluate the last source of lead exposure and particularly only for ambient air lead levels. Air lead measurements were available during the entire study period for only one station which was located on the west side of Manhattan at a height of 56 m. Superposition of the air lead and blood lead levels indicated a similarity in cycle and decline. The authors cautioned against overinterpretation by assuming that one air monitoring site was representative of the air lead exposure of New York City residents. With this in mind, the investigators fitted a multiple regression model to the data to try to define the important determinants of blood lead levels for this population. Age, ethnic group and air lead level were all found to be significant determinants of blood lead levels. The authors further point out the possibility of a change in the nature of the population being screened before and after 1973. They reran this regression analysis separately for years both before and after 1973. The same results were still obtained, although the exact coefficients varied.

Billick et al. (1980) extended their previous analysis of the data from the single monitoring site mentioned earlier. The investigators examined the possible relationship between blood lead level and the amount of lead in gasoline used in the area. Figures 11-26 and 11-27 present illustrative trend lines in blood leads for blacks and Hispanics, vs. air lead and

TABLE 11-55. CALCULATED BLOOD LEAD UPTAKE FROM AIR LEAD USING MANTON ISOTOPE STUDY

Subject	Concentration	Exposure*	Deposition	Absorption	Blood Uptake from Air: Calculated Inhalation	Blood Uptake from Air: Observed	Fraction of lead uptake from gasoline by direct inhalation
5	0.22 μg/m^3	15 m^3/day	37%	50%	0.61 μg/d	5.1 μg/d	0.120
6	1.09 μg/m^3	15 m^3/day	37%	50%	3.0 μg/d	13.2 μg/d	0.229
9	0.45 μg/m^3	15 m^3/day	37%	50%	1.2 μg/d	9.9 μg/d	0.126

*assumed rather than measured exposure, deposition and absorption.

Source: Stephens, 1981, based on Manton, 1977; Table III.

gasoline lead, respectively. Several different measures of gasoline lead were tried: mid-Atlantic Coast (NY, NJ, Conn), New York, New York plus New Jersey and New York plus Connecticut. The lead in gasoline trend line appears to fit the blood lead trend line better than the air lead trend, especially in the summer of 1973.

Multiple regression analyses were calculated using six separate models. The best fitting model had an $R^2 = 0.745$. Gasoline lead content was included rather than air lead. The gasoline lead content coefficient was significant for all three racial groups. The authors state a number of reasons for gasoline lead providing a better fit than air lead, including the fact that the single monitoring site might not be representative.

Nathanson and Nudelman (1980) provide more detail regarding air lead levels in New York City. In 1971, New York City began to regulate the lead content of gasoline sold. Lead in gasoline was to be totally banned by 1974, but supply and distribution problems delayed the effect of the ban. Ultimately regulation of lead in gasoline was taken over by the U.S. Environmental Protection Agency.

New York City measured air lead levels during the periods June 1969 to September 1973 and during 1978 at multiple sites. The earlier monitoring was done by 40 rooftop samples using cellulose filters analyzed by AAS. The latter sampling was done by 27 rooftop samplers using glass fiber filters analyzed by X-ray fluorescence (XRF). There was excellent agreement between the XRF and atomic absorption analyses for lead ($r = 0.985$). Furthermore, the XRF analyses were checked against EPA AAS and again excellent agreement was found. The authors did, however, point out that cellulose filters are not as efficient as glass fiber filters. Therefore, the earlier results tend to be underestimates of air lead levels.

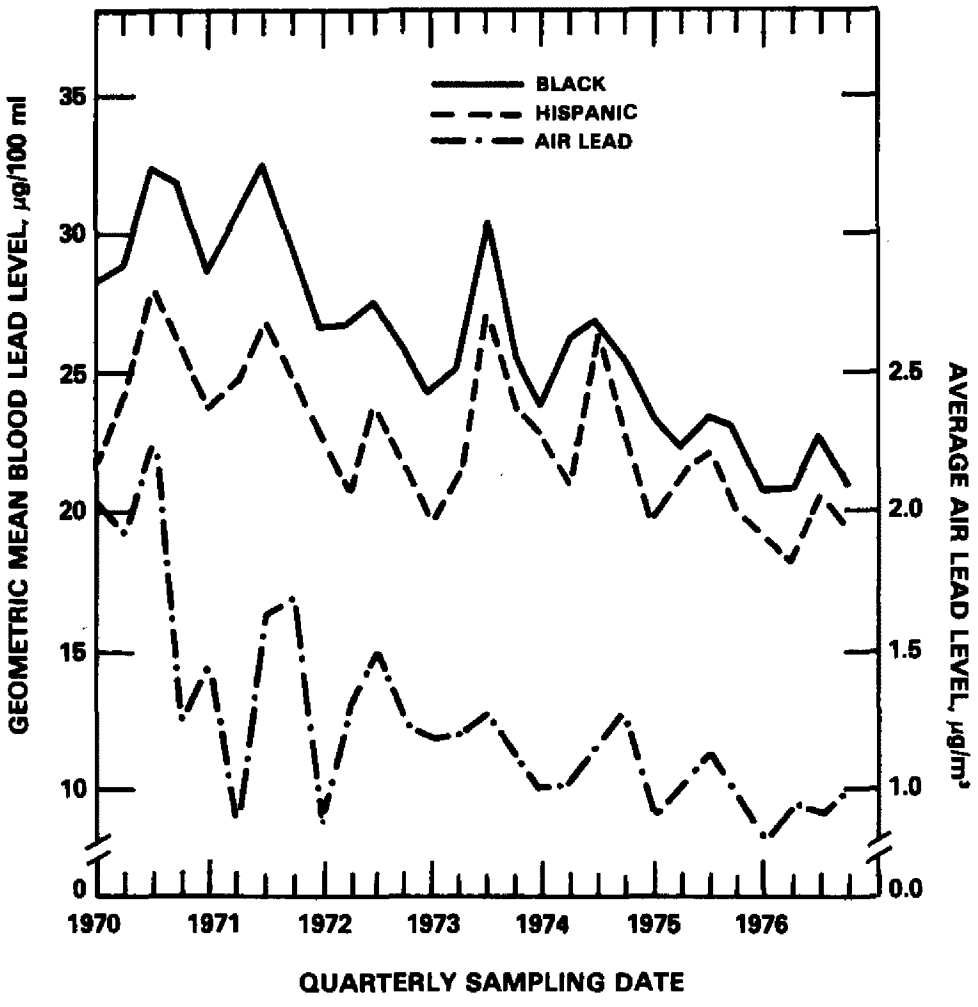

Figure 11-26. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and ambient air lead concentration versus quarterly sampling period, 1970-1976.

Source: Billick (1980).

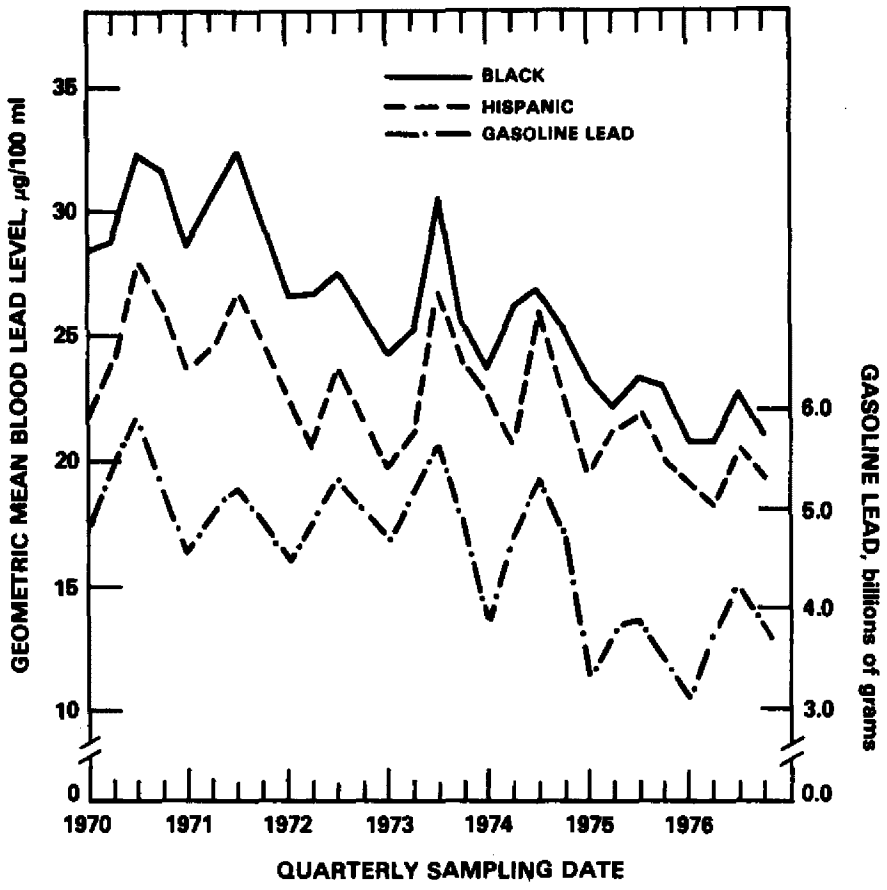

Figure 11-27. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and estimated amount of lead present in gasoline sold in New York, New Jersey, and Connecticut versus quarterly sampling period, 1970-1976.

Source: Billick (1980).

Quarterly citywide air lead averages generally declined during the years 1969-1978. The maximum quarterly citywide average obtained was about 2.5 $\mu g/m^3$ for the third quarter of 1970. The citywide trend corresponds to the results obtained from the single monitoring site used in Billick et al.'s analysis. The citywide data suggest that the single monitoring site in Manhattan is a responsible indicator of air lead level trends. The graph in Figure 11-28 reinforces this assertion by displaying the geometric mean blood lead levels for blacks and Hispanics in the 25 to 36-month age groups and the quarterly citywide air lead levels for the periods of interest. A good correspondence was noted.

As part of a detailed investigation of the relationship of blood lead levels and lead in gasoline covering three cities, Billick (1982) extended the time trend analyses of New York City blood lead data. Figure 11-29 presents the time trend line for geometric mean blood leads for blacks age 24-35 months extended to 1979. The downward trend noted earlier was still continuing, although the slopes for both the blood and gasoline lead seem to be somewhat shallower toward the most recent data. A similar picture is presented by the percent of children with blood lead levels greater than 30 µg/dl. In the early 70's, about 60 percent of the screened children had these levels; by 1979 the percent had dropped between 10 and 15 percent.

11.5.1.3 NHANES II. Blood lead data from the second National Health and Nutrition Examination Survey has been described in sections 11.3.3.1 and 11.3.4.4. The report by Annest et al. (1983) found highly significant associations between amounts of lead used in gasoline production in the U.S. and blood lead levels. The associations persisted after adjusting for race, sex, age, region of the country, season, income and degree of urbanization.

Various analyses of the relationship between blood lead values in the NHANES II sample and estimated gasoline lead usage were also reviewed by an expert panel (see Appendix 11-D). They concluded that the correlation between gasoline lead usage and blood lead levels was consistent with the hypothesis that gasoline lead is an important causal factor, but the analyses did not actually confirm the hypothesis.

11.5.1.4 Frankfurt, West Germany. Sinn (1980; 1981) conducted a study specifically examining the environmental and biological impact of the gasoline lead phasedown implemented in West Germany on January 1, 1976. Frankfurt am Main provided a good setting for such a study because of its physical character.

Air and dustfall lead levels at several sites in and about the city were determined before and after the phasedown was implemented. The mean air lead concentrations obtained during the study are presented in Table 11-56. A substantial decrease in air lead levels was noted for the low level high traffic site (3.18 $\mu g/m^3$ in 1975-76 to 0.68 $\mu g/m^3$ in 1978-79). No change was noted for the background site while only minor changes were observed for the other locations. Dustfall levels fell markedly (218 $mg/cm^2 \cdot day$ for 1972-73 to 128 $mg/cm^2 \cdot day$

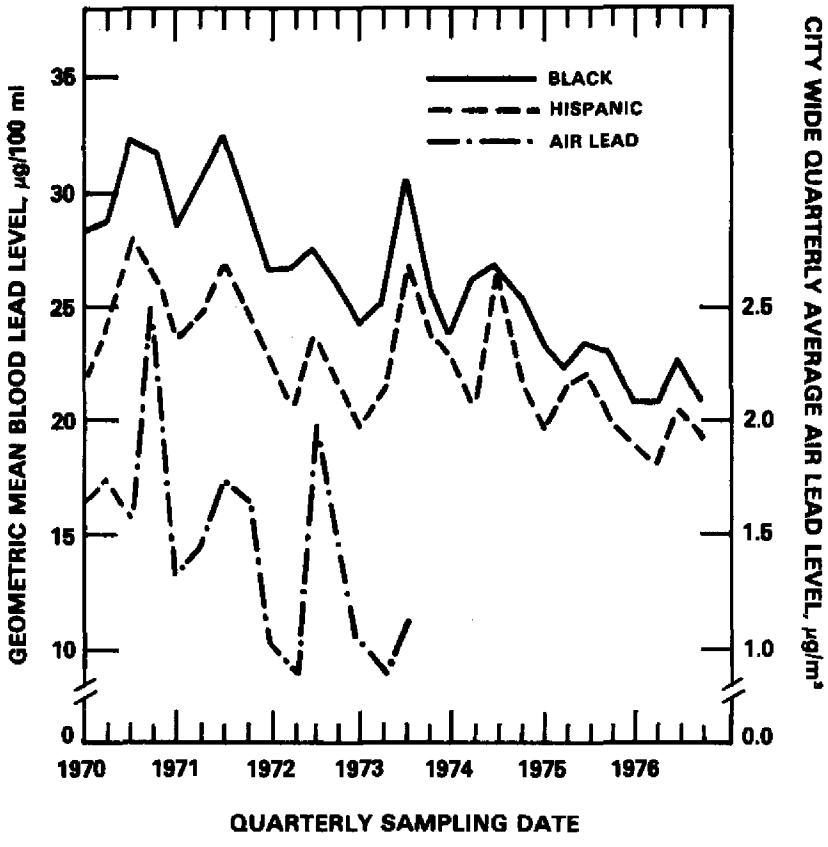

Figure 11-28. Geometric mean blood levels for blacks and Hispanics in the 25-to-36-month age group and rooftop quarterly averages for ambient citywide lead levels.

Source: Nathanson and Nudelman (1980).

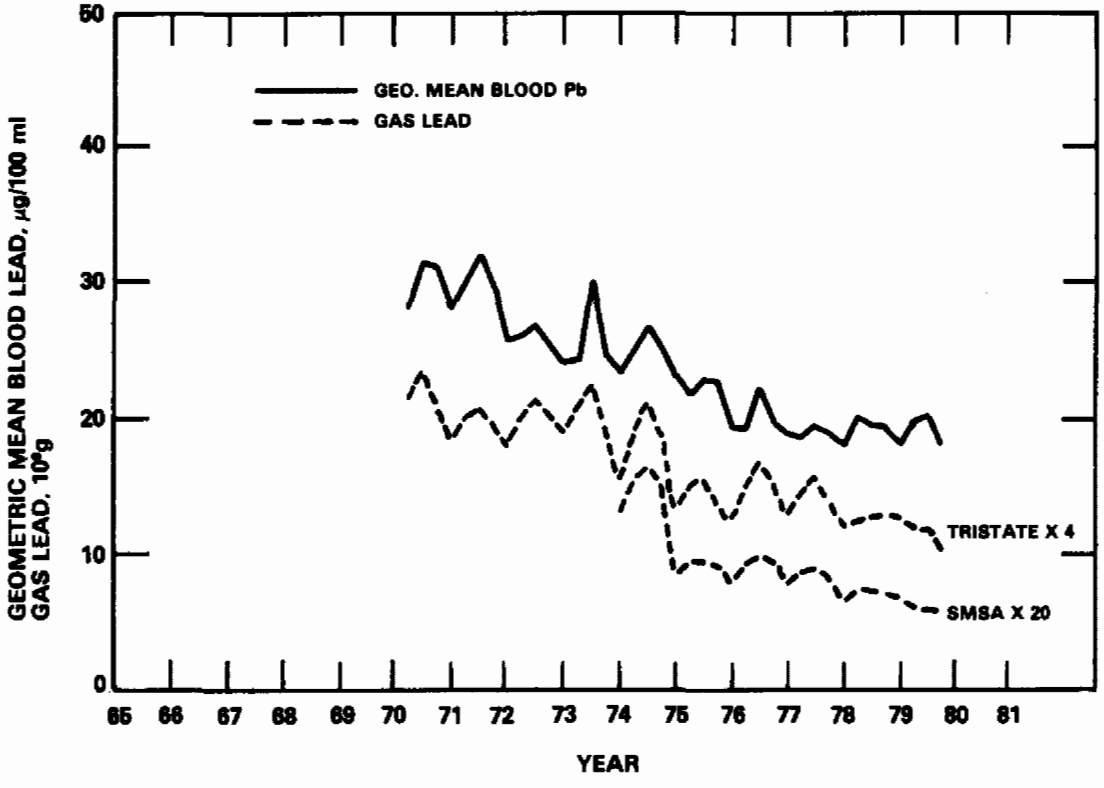

Figure 11-29. Time dependence of blood lead and gas lead for blacks, aged 24 to 35 months, in New York.

So ·ce: Billick (1982).

Source: Billick (1982).

TABLE 11-56. MEAN AIR LEAD CONCENTRATIONS DURING THE VARIOUS BLOOD SAMPLING PERIODS AT THE MEASUREMENT SITES DESCRIBED IN THE TEXT ($\mu g/m^3$)

	Residential Low Traffic	High Traffic (>20m)	High Traffic (3m)	Background Site
1975-1976	0.57	0.59	3.18	0.12
1976-1977	0.39	0.38	1.04	0.09
1977-1978	0.32	0.31	0.66	0.10
1978-1979	0.39	0.31	0.68	0.12

Source: Sinn (1980, 1981).

for 1977-78). Traffic counts were essentially unchanged in the area during the course of study.

A number of population groups were included in the study of the blood lead levels; they were selected for having either occupational or residential exposure to high density automobile traffic. Blood samples were taken serially throughout the study (three phases in December-January 1975-76, December-January 1976-77 and December-January 1977-78). Blood samples were collected by venipuncture and analyzed by three different laboratories. All the labs used AAS although sample preparation procedures varied. A quality control program across the laboratories was conducted. Due to differences in laboratory analyses, attrition and loss of sample, the number of subjects who could be examined throughout the study was considerably reduced from the initial number recruited (124 out of 300).

Preliminary analyses indicated that the various categories of subjects had different blood lead levels, and that males and females within the same category differed. A very complicated series of analyses then ensued that made it difficult to draw conclusions because the various years' results were displayed separately by each laboratory performing the chemical analysis and by different groupings by sex and category. In Sinn's later report (1981) a downward trend was shown to exist for males and females who were in all years of the study and whose blood levels were analyzed by the same laboratory.

11.5.2 Primary Smelters Populations

Most studies of nonindustry-employed populations living in the vicinity of industrial sources of lead pollution were triggered because evidence of severe health impairment had been found. Subsequently, extremely high exposures and high blood lead concentrations were found. The following studies document the excessive lead exposure that developed, as well as some of the relationships between environmental exposure and human response.

11.5.2.1 El Paso, Texas. In 1972, the Centers for Disease Control studied the relationships between blood lead levels and environmental factors in the vicinity of a primary smelter located in El Paso, Texas emitting lead, copper and zinc. The smelter had been in operation since the late 1800's (Landrigan et al., 1975; U.S. Centers for Disease Control, 1973). Daily Hi-Vol samples collected on 86 days between February and June 1972 averaged 6.6 $\mu g/m^3$. These air lead levels fell off rapidly with distance, reaching background values approximately 5 km from the smelter. Levels were higher downwind, however. High concentrations of lead in soil and house dusts were found, with the highest levels occurring near the smelter. The geometric means of 82 soil and 106 dust samples from the sector closest to the smelter were 1791 and 4022 µg/g, respectively. Geometric means of both soil and dust lead levels near the smelter were significantly higher than those in study sectors 2 or 3 km farther away.

Sixty-nine percent of children 1- to 4-years old living near the smelter had blood lead levels greater than 40 µg/dl, and 14 percent had blood lead levels that exceeded 60 µg/dl. Concentrations in older individuals were lower; nevertheless, 45 percent of the children 5- to 9-years old, 31 percent of the individuals 10- to 19-years old and 16 percent of the individuals above 19 had blood lead levels exceeding 40 µg/dl. The data presented preclude calculations of means and standard deviations.

Data for people aged 1 to 19 years of age living near the smelter showed a relationship between blood lead levels and concentrations of lead in soil and dust. For individuals with blood lead levels greater than 40 µg/dl, the geometric mean concentration of lead in soil at their homes was 2587 µg/g, whereas for those with a blood lead concentration less than 40 µg/dl, home soils had a geometric mean of 1419 µg/g. For house dust, the respective geometric means were 6447 and 2067 µg/g. Length of residence was important only in the sector nearest the smelter.

Additional sources of lead were also investigated. A relationship was found between blood lead concentrations and lead release from pottery, but the number of individuals exposed to lead-glazed pottery was very small. No relationships were found between blood lead levels and hours spent out of doors each day, school attendance, or employment of a parent at the smelter. The reported prevalence of pica also was minimal.

Data on dietary intake of lead were not obtained because there was no food available from sources near the smelter since the climate and proximity to the smelter prevented any farming in the area. It was unlikely that the dietary lead intakes of the children from near the smelter or farther away were significantly different. It was concluded that the primary factor associated with elevated blood lead levels in the children was ingestion or inhalation of dust containing lead.

Morse et al. (1979) conducted a follow-up investigation of the El Paso smelter to determine whether the environmental controls instituted following the 1972 study had reduced the

lead problem described. In November 1977, all children 1- to 18-years old living within 1.6 km of the smelter on the U.S. side of the border were surveyed. Questionnaires were administered to the parents of each participant to gather background data.

Venous blood samples were drawn and analyzed for lead by modified Delves cup spectrophotometry. House dust and surface soil samples, as well as sample pottery items were taken from each participant's residence. Dust and soil samples were analyzed for lead by AAS. Pottery lead determinations were made by the extraction technique of Klein. Paint, food, and water specimens were not collected because the earlier investigations of the problem had demonstrated these media contributed little to the lead problem in El Paso.

Fifty-five of 67 families with children (82 percent) agreed to participate in the study. There were 142 children examined in these homes. The homes were then divided into two groups. Three children lived in homes within 0.8 km of the smelter. Their mean blood lead level in 1977 was 17.7 μg/dl. By contrast, the mean blood lead level of 160 children who lived within 0.8 km of the smelter in 1972 had been 41.4 μg/dl. In 1977, 137 children lived in homes located 0.8 to 1.6 km from the smelter. Their mean blood lead level was 20.2 μg/dl. The mean blood level of 96 children who lived in that same area in 1972 had been 31.2 μg/dl.

Environmental samples showed a similar improvement. Dust lead fell from 22,191 μg/g to 1,479 μg/g while soil lead fell from 1,791 μg/g to 427 μg/g closest to the smelter. The mean air lead concentration at 0.4 km from the smelter decreased from 10.0 to 5.5 $\mu g/m^3$ and at 4.0 km from 2.1 to 1.7 $\mu g/m^3$. Pottery was not found to be a problem.

11.5.2.2 CDC-EPA Study. Baker et al. (1977b), in 1975, surveyed 1774 children 1 to 5 years old, most of whom lived within 4 miles of lead, copper or zinc smelters located in various parts of the United States. Blood lead levels were modestly elevated near 2 of the 11 copper and 2 of the 5 zinc smelters. Although blood lead levels in children were not elevated in the vicinity of three lead smelters, their FEP levels were somewhat higher than those found in controls. Increased levels of lead and cadmium in hair samples were found near lead and zinc smelters; this was considered evidence of external exposure. No environmental determinations were made for this study.

11.5.2.3 Meza Valley, Yugoslavia. A series of Yugoslavian studies investigated exposures to lead from a mine and a smelter in the Meza Valley over a period of years (Fugas et al., 1973; Graovac-Leposavic et al. 1973; Milic et al., 1973; Djuric et al., 1971, 1972). In 1967, 24-hour lead concentrations measured on 4 different days varied from 13 to 84 $\mu g/m^3$ in the village nearest the smelter, and concentrations of up to 60 $\mu g/m^3$ were found as far as 5 km from the source. Mean particle size in 1968 was less than 0.8 μm. Analysis of some common foodstuffs showed concentrations that were 10 to 100 times higher than corresponding foodstuffs from the least exposed area (Mezica) (Djuric et al., 1971). After January 1969, when

partial control of emissions was established at the smelter, weighted average weekly exposure was calculated to be 27 $\mu g/m^3$ in the village near the smelter. In contrast to this, the city of Zagreb (Fugas et al., 1973), which has no large stationary source of lead, had an average weekly air lead level of 1.1 $\mu g/m^3$.

In 1968, the average concentration of ALA in urine samples from 912 inhabitants of 6 villages varied by village from 9.8 to 13 mg/l. A control group had a mean ALA of 5.2 mg/l. Data on lead in blood and the age and sex distribution of the villagers were not given (Djuric et al., 1971).

Of the 912 examined, 559 had an ALA level greater than 10 mg/l of urine. In 1969, a more extensive study of 286 individuals with ALA greater than 10 mg/l was undertaken (Graovac-Leposavic et al. 1973). ALA-U increased significantly from the previous year. When the published data were examined closely, there appeared to be some discrepancies in interpretation. The exposure from dust and from food might have been affected by the control devices, but no data were collected to establish this. In one village, Zerjua, ALA-U dropped from 21.7 to 9.4 mg/l in children 2 to 7 years of age. Corresponding ALA-U values for 8- to 15-year-olds and for adult men and women were reduced from 18.7 to 12.1, from 23.9 to 9.9 and from 18.5 to 9.0 mg/l, respectively. Because lead concentrations in air (Fugas et al., 1973), even after 1969, indicated an average exposure of 25 $\mu g/m^3$, it is possible that some other explanation should be sought. The author indicated in the report that the decrease in ALA-U showed "the dependence on meteorologic, topographic, and technological factors" (Graovac-Leposavic et al., 1973).

Fugas (1977) in a later report estimated the time-weighted average exposure of several populations studied during the course of this project. Stationary samplers as well as personal monitors were used to estimate the exposure to airborne lead for various parts of the day. These values were then coupled with estimated proportions of time at which these exposure held. In Table 11-57, the estimated time-weighted air lead values as well as the observed mean blood lead levels for these studied populations are presented. An increase in blood lead values occurs with increasing air lead exposure.

11.5.2.4 Kosovo Province, Yugoslavia. Residents living in the vicinity of the Kosovo smelter were found to have elevated blood lead levels (Popovac et al., 1982). In this area of Yugoslavia, five air monitoring stations had been measuring air lead levels since 1973. Mean air lead varied from 7.8 to 21.7 $\mu g/m^3$ in 1973; by 1980 the air lead averages ranged from 21.3 to 29.2 $\mu g/m^3$. In 1978 a pilot study suggested that there was a significant incidence of elevated blood lead levels in children of the area. Two major surveys were then undertaken.

In August 1978 letters were sent to randomly selected families from the business community, hospitals or lead-related industries in the area. All family members were asked to come

TABLE 11-57. MEAN BLOOD LEAD LEVELS IN SELECTED YUGOSLAVIAN POPULATIONS, BY ESTIMATED WEEKLY TIME-WEIGHTED AIR LEAD EXPOSURE

Population	N	Time-weighted air lead, $\mu g/m^3$	Blood lead level, $\mu g/dl$	SD
Rural I	49	0.079	7.9	4.4
Rural II	47	0.094	11.4	4.8
Rural III	45	0.146	10.5	4.0
Postmen	44	1.6	18.3	9.3
Customs officers	75	1.8	10.4	3.3
Street car drivers	43	2.1	24.3	10.5
Traffic policemen	24	3.0	12.2	5.1

Source: Fugas, 1977.

to a hospital for primary screening by erythrocyte protoporphyrin. A central population of comparable socioeconomic and dietary background was collected from a town without lead emissions. Blood levels were determined primarily for persons with greater than µg/g Hgb. EP was measured by a hematofluorimeter, while blood lead was determined by the method of Fernandez using atomic absorption with graphite furnace and background correction.

Mean EP values were higher in the 1978 survey for exposed residents compared to controls in the average age group. EP values seemed to decline with age. Similar differences were noted for blood lead levels. The observed mean blood leads, ranging from 27.6 in the greater than 15-year age group to 50.9 µg/dl in the 5- to 10-year group, suggest substantial lead exposure of these residents. In the control group the highest blood lead level was 19 µg/dl. In December 1980 a second survey was conducted to obtain a more representative sample of persons residing in the area. Letters were sent again, and 379 persons responded. EP levels were higher in all ages in 1980 vs. 1978, although the differences were not statistically significant. The air lead levels increased from 14.3 $\mu g/m^3$ in 1978 to 23.8 $\mu g/m^3$ in 1980.

Comparing the 1980 blood lead results with the 1978 control group shows that the 1980 levels were higher in each age group. Males older than 15 years had higher mean blood lead levels than the females (39.3 vs. 32.4 µg/dl).

11.5.2.5 The Cavalleri Study. Cavalleri et al. (1981) studied children in the vicinity of a lead smelter and children from a control area (4 km from the smelter). The exposed population consisted of 85 children aged 3 to 6 attending a nursery school and 80 primary school children

aged 8 to 11. The control population was 25 nursery school children aged 3 to 6 and 64 primary school children aged 8 to 11. Since the smelter had installed filters 8 years before the study, the older children living in the smelter area had a much higher lifetime exposure.

Blood lead analysis was performed on venous samples using anodic stripping voltammetry by Morrell's method. Precision was checked over the range 10 to 100 µg/dl. Reported reproducibility was also good. All samples were subsequently reanalyzed by AAS using graphite furnace and background correction by the method of Volosen. The average values obtained by the second method were quite similar to those of the first (average difference 1.4 µg/dl; correlation coefficient, 0.962).

Air was sampled for lead for 1 month at three sampling sites. The sites were located at 150 m, 300 m and 4 km from the wall of the lead smelter. The average air lead levels were 2.32, 3.43 and 0.56 $\mu g/m^3$, respectively.

A striking difference in blood lead levels of the exposed and control populations was observed; levels in the exposed population were almost twice that in the control population. There was no significant difference between nursery school and primary school children. The geometric mean for nursery school children was 15.9 and 8.2 for exposed and control, respectively. For primary school it was 16.1 and 7.0 µg/dl. In the exposed area 23 percent of the subjects had blood lead levels between 21 and 30 µg/dl and 3 percent greater than 31 µg/dl. No control children had PbB greater than 20 µg/dl. The air leads were between 2 to 3 $\mu g/m^3$ in the exposed and 0.56 $\mu g/m^3$ in the control cases.

11.5.3 Battery Plants

Studies of the effects of storage battery plants have been reported from France and Italy (Dequidt et al., 1971; De Rosa and Gobbato, 1970). The French study found that children from an industrialized area containing such a plant excreted more ALA than those living in a different area (Dequidt et al., 1971). Increased urinary excretion of lead and coproporphyrins was found in children living up to 100 m from a battery plant in Italy (De Rosa and Gobbato, 1970). Neither study gave data on plant emissions or lead in air.

Zielhius et al. (1979) studied children living in the vicinity of the Arnhem secondary lead smelter. In 1976 they recruited children to serve as subjects and controls. The children chosen were 2 and 3 years old. Parents were asked to complete a questionnaire for background information. Two ml venous samples were collected from 17 children living less than 1 km, from 54 children living 1 to 2 km, and from 37 children living greater than 2 km from the smelter (control group). Blood samples were analyzed for lead by graphite furnace AAS and for FEP by the method of Piomelli. Air measurements for lead were made in autumn 1976. Samples were established about 2 km northeast and about 0.4 km north of the plant. Air lead levels ranged from 0.8 to 21.6 $\mu g/m^3$ northeast and from 0.5 to 2.5 $\mu g/m^3$ north of the plant.

Blood leads were statistically significantly higher closer to the smelter. For all children the mean blood lead level was 19.7 µg/dl for the less than 1 km and 11.8 µg/dl for the controls (>2 km). Similarly, FEP levels were higher for the closer (41.9 µg/100 ml RBC) children as opposed to the control (32.5 µg/100 ml RBC). Higher blood levels were associated with lower socioeconomic status.

Further investigation of this smelter was undertaken by Brunekreef et al. (1981) and Diemel et al. (1981). In May 1978 venipuncture blood samples were collected from 95 one- to three-year old children living within 1 km of the smelter. Blood leads were determined by graphite AAS.

Before the blood sampling, an environmental sampling program was conducted. The samples collected are listed in Table 11-58. Questionnaires were administered to collect background and further exposure information. A subset of 39 children was closely observed for 1 or 2 days for mouthing behavior. Table 11-58 also presents the overall results of the environmental sampling. As can be readily seen, there is a low exposure to airborne lead (G.M. 0.41 µg/m^3 with a range of 0.28 to 0.52 µg/m^3). Soil exposure was moderate, although high. Interior dust was high in lead, geometric mean of 967 µg/g with a maximum of 4741 µg/g. In a few homes, high paint lead levels were found. Diemel et al. (1981) extended the analysis of the environmental samples. They found that indoor pollution was lower than outside. In Arnhem, it was found that lead is carried into the homes in particulate form by sticking to shoes. Most of the lead originated from soil from gardens and street dust.

Simple correlation coefficients were calculated to investigate the relationship between log blood lead and the independent variables. Significantly, correlations were found with quantity of house dust, quantity of deposited lead indoors, observational score of dustiness, age of child and the average number of times an object is put in the mouth. Multiple regression analyses were calculated on four separate subpopulations. Among children living in houses with gardens, the combination of soil lead level and educational level of the parents explained 23 percent of the variations of blood lead. In children without gardens, the amount of deposited lead indoors explained 26 percent of the variance. The authors found that an increase in soil lead level from 100 to 600 µg/g results in an increase in blood lead of 63 µg/dl.

TABLE 11-58. ENVIRONMENTAL PARAMETERS AND METHODS: ARNHEM LEAD STUDY, 1978[a]

Parameter	Method	Geometric Mean	Range
1. Lead in ambient air ($\mu g/m^3$)	High volume samples; 24-hr measurements at 6 sites, continuously for 2 months	0.41	0.28-0.52
2. Lead in dustfall ($\mu g/m^3 \cdot day$)	Standard deposit gauges; 7-day measurements at 22 sites, semicontinuously for 3 months	467	108-2210
3. Lead in soil ($\mu g/g$)	Sampling in gardens of study populations; analysis of layers from 0 to 5 cm and 5 to 20 cm	240	21-1126
4. Lead in street dust ($\mu g/g$)	Samples at 31 sites, analysis of fraction <0.3mm	690	77-2667
5. Lead in indoor air ($\mu g/m^3$)	Low volume samples; 1-month measurements in homes of study population, continuously for 2 months	0.26	0.13-0.74
6. Lead in dustfall indoors ($\mu g/m^3 \cdot day$)	Greased glass plates of 30 x 40 cm; 1-month measurements in homes of study population, continuously for 3 months	7.34	1.36-42.35
7. Lead in floor dust ($\mu g/g$)	Vacuum cleaner with special filter holder; 5 samples, collected on 3 different occasions; with intervals of approximately 1 month, in homes of study populations	fine 957 course 282	463-4741 117-5250
8. Easily available lead indoors	Wet tissues, 1 sample in homes of study population	85% of samples	<20 µg Pb/tissue
9. Lead in tapwater	Proportional samples, during 1 week in homes of study population	5.0 (arthimetic) mean	<0.5-90.0
10. Dustiness of homes	Visual estimation, on a simple scale ranging from 1 (clean) to 3 (dusty); 6 observations in homes of study population		

[a]All lead analyses were performed by atomic absorption spectrophotometry, except part of the tapwater analysis, which was performed by anodic stripping voltametry. Lead in tapwater analyzed by the National Institute of Drinking Water Supply in Leidscherdam. Soil and street dust analyzed by the Laboratory of Soil and Plant Research in Oosterbeek. (Zielhuis, et. al., 1979; Diemel, et. al., 1981)

11.5.4 Secondary Smelters

In a Dallas, Texas, study of two secondary lead smelters, the average blood lead levels of exposed children was found to be 30 μg/dl vs. an average of 22 μg/dl in control children (Johanson and Luby, 1972). For the two study populations, the air and soil lead levels were 3.5 and 1.5 $\mu g/m^3$ and 727 and 255 μg/g, respectively.

In Toronto, Canada the effects of two secondary lead smelters on the blood and hair lead levels of nearby residents have been extensively studied (Ontario Ministry of the Environment, 1975; Roberts et al., 1974). In a preliminary report, Roberts et al. (1974) stated that blood and hair lead levels were higher in children living near the two smelters than in children living in an urban control area. Biologic and environmental lead levels were reported to decrease with increasing distance from the base of the smelter stacks.

A later and more detailed report identified a high rate of lead fallout around the two secondary smelters (Ontario Ministry of the Environment, 1975). Two groups of children living within 300 m of each of the smelters had geometric mean blood lead levels of 27 and 28 μg/dl, respectively; the geometric mean for 1231 controls was 17 μg/dl. Twenty-eight percent of the sample children tested near one smelter during the summer and 13 percent of the sample children tested near the second smelter during the winter had blood lead levels greater than 40 μg/dl. Only 1 percent of the controls had blood lead levels greater than 40 μg/dl. For children, blood lead concentrations increased with proximity to both smelters, but this trend did not hold for adults, generally. The report concluded that soil lead levels were the main determinant of blood lead levels; this conclusion was disputed by Horn (1976).

Blood lead levels in 293 Finnish individuals, aged 15 to 80, were significantly correlated with distance of habitation from a secondary lead smelter (Nordman et al., 1973). The geometric mean blood lead concentration for 121 males was 18.1 μg/dl; for 172 females, it was 14.3 μg/dl. In 59 subjects who spent their entire day at home, a positive correlation was found between blood lead and distance from the smelter up to 5 km. Only one of these 59 individuals had a blood lead greater than 40 μg/dl, and none exceeded 50 μg/dl.

11.5.5 Secondary Exposure of Children

Excessive intake and absorption of lead on the part of children can result when parents who work in a dusty environment with a high lead content bring dust home on their clothes, shoes or even their automobiles. Once they are home, their children are exposed to the dust.

Landrigan et al. (1976) reported that the 174 children of smelter workers who lived within 24 km of the smelter had significantly higher blood lead levels, a mean of 55.1 μg/dl, than the 511 children of persons in other occupations who lived in the same areas whose mean

blood lead levels were 43.7 µg/dl. Analyses by EPA of the data collected in Idaho showed that employment of the father at a lead smelter, at a zinc smelter, or in a lead mine resulted in higher blood lead levels in the children living in the same house as opposed to those children whose fathers were employed in different locations (Table 11-59). The effect associated with parental employment appears to be much more prominent in the most contaminated study areas nearest to the smelter. This may be the effect of an intervening socioeconomic variable: the lowest paid workers, employed in the highest exposure areas within the industry, might be expected to live in the most undesirable locations, closest to the smelter.

TABLE 11-59. GEOMETRIC MEAN BLOOD LEAD LEVELS FOR CHILDREN BASED ON REPORTED OCCUPATION OF FATHER, HISTORY OF PICA, AND DISTANCE OF RESIDENCE FROM SMELTER

Area	Distance from smelter, km	Lead smelter worker		Lead/zinc mine worker		Zinc smelter worker		Other occupations	
		Pica	No Pica	Pica	No Pica	Pica	No Pica	Pica	No Pica
1	1.6	78.7	74.2	75.3	63.9	69.7	59.1	70.8	59.9
2	1.6 to 4.0	50.2	52.2	46.9	46.9	62.7	50.3	37.2	46.3
3	4.0 to 10.0	33.5	33.3	36.7	33.5	36.0	29.6	33.3	32.6
4	10.0 to 24.0	-	30.3	38.0	32.5	40.9	36.9	-	39.4
5	24.0 to 32.0	-	24.5	31.8	27.4	-	-	28.0	26.4
6	75	-	-	-	-	-	-	17.3	21.4

Source: Landrigan et al. 1976.

Landrigan et al. (1976) also reported a positive history of pica for 192 of the 919 children studied in Idaho. This history was obtained by physician and nurse interviews of parents. Pica was most common among 2-year old children and only 13 percent of those with pica were above age 6. Higher blood lead levels were observed in children with pica than in those without pica. Table 11-59 shows the mean blood lead levels in children as they were affected by pica, occupation of the father and distance of residence from the smelter. Among the populations living nearest to the smelter environmental exposure appears to be sufficient at times to more than overshadow the effects of pica, but this finding may also be caused by inadequacies inherent in collecting data on pica.

These data indicate that in a heavily contaminated area, blood lead levels in children may be significantly increased by the intentional ingestion of nonfood materials having a high lead content.

Data on the parents' occupation are, however, more reliable. It must be remembered also that the study areas were not homogeneous socioeconomically. In addition, the specific type of work an individual does in an industry is probably much more important than simply being employed in a particular industry. The presence in the home of an industrial employee exposed occupationally to lead may produce increases in the blood lead levels ranging from 10 to 30 percent.

The importance of the infiltration of lead dusts onto clothing, particularly the undergarments, of lead workers and their subsequent transportation has been demonstrated in a number of studies on the effects of smelters (Martin et al., 1975). It was noted in the United Kingdom that elevated blood lead levels were found in the wives and children of workers, even though they resided some considerable distance from the facility. It was most prominent in the workers themselves who had elevated blood lead levels. Quantities of lead dust were found in workers' cars and homes. It apparently is not sufficient for a factory merely to provide outer protective clothing and shower facilities for lead workers. In another study in Bristol, from 650 to 1400 μg/g of lead was found in the undergarments of workers as compared with 3 to 13 μg/g in undergarments of control subjects. Lead dust will remain on the clothing even after laundering: up to 500 mg of lead has been found to remain on an overall garment after washing (Lead Development Association, 1973).

Baker et al. (1977a) found blood lead levels greater than 30 μg/dl in 38 of 91 children whose fathers were employed at a secondary lead smelter in Memphis, TN, House dust, the only source of lead in the homes of these children, contained a mean of 2687 μg/g compared with 404 μg/g in the homes of a group of matched controls. Mean blood lead levels in the workers' children were significantly higher than those for controls and were closely correlated with the lead content of household dust. In homes with lead in dust less than 1000 μg/g, 18 children had a mean blood lead level of 21.8 ± 7.8 μg/dl, whereas in homes where lead in dust was greater than 7000 μg/g, 6 children had mean blood lead levels of 78.3 ± 34.0 μg/dl. See Section 7.3.2.1.6 for a further discussion of household dust.

Other studies have documented increased lead absorption in children of families where at least one member was occupationally exposed to lead (Fischbein et al., 1980a). The occupational exposures involved battery operations (Morton et al., 1982; U.S. Centers for Disease Control, 1977b; Dolcourt et al., 1978, 1981; Watson et al., 1978; Fergusson et al., 1981) as well as other occupations (Snee, 1982b; Rice et al., 1978).

In late summer of 1976, a battery plant in southern Vermont provided the setting for the first documented instance of increased lead absorption in children of employees in the battery industry. The data were first reported by U.S. Centers for Disease Control (1977b) and more completely by Watson et al. (1978).

Reports of plant workers exposed to high levels of lead stimulated a study of plant employees and their children in August and September 1975. In the plant, lead oxide powder is used to coat plates in the construction of batteries. Before the study, the work setting of all 230 employees of the plant had been examined and 62 workers (22 percent) were identified as being at risk for high lead exposure. All of the high risk workers interviewed reported changing clothes before leaving work and 90 percent of them reported showering. However, 87 percent of them stated that their work clothes were washed at home.

Of the high risk employees, 24 had children between the ages of 1 and 6 years. A case-control study was conducted in the households of 22 of these employees. Twenty-seven children were identified. The households were matched with neighborhood controls including 32 control children. None of the control family members worked in a lead industry. Capillary blood specimens were collected from all children and the 22 battery plant employees had venous specimens taken. All blood samples were analyzed for lead by AAS. Interviewers obtained background data, including an assessment of potential lead exposures.

About 56 percent of the employees' children had blood leads greater than 30 µg/dl compared with about 13 percent of the control children. Mean blood lead levels were statistically significantly different, 31.8 µg/dl and 21.4 µg/dl, respectively. Blood lead levels in children were significantly correlated with employee blood lead levels.

House dust lead levels were measured in all children's homes. Mean values were 2239.1 µg/g and 718.2 µg/g for employee and control homes, respectively; this was statistically significant. Examination of the correlation coefficient between soil lead and blood lead levels in the two sets of homes showed a marginally significant coefficient in the employee household but no correlation in the control homes. Tap water and paint lead levels did not account for the observed difference in blood leads between children of workers and neighborhood controls. It is significant that these findings were obtained despite the changing of clothes at the plant.

Morton et al. (1982) conducted their study of children of battery plant workers and controls during February-March 1978. Children were included in the study if one parent had at least 1 year of occupational exposure, if they had lived at the same residence for at least 6 months, and if they were from 12-83 months of age. Children for the control group had to have no parental occupational exposure to lead for 5 years, and had to have lived at the same address at least 6 months.

Thirty-four children were control matched to the exposed group by neighborhoods and age (±1 year). No matching was thought necessary for sex because in this age group blood lead levels are unaffected by sex. The selection of the control population attempted to adjust for both socioeconomic status as well as exposure to automotive lead.

Capillary blood specimens were collected concurrently for each matched pair. Blood lead levels were measured by the CDC lab using a modified Delves cup AAS procedure. Blood lead levels for the employees for the previous year were obtained from company records. Questionnaires were administered at the same time as the blood sampling to obtain background information. The homemaker was asked to complete the interview to try to get a more accurate picture of the hygiene practices followed by the employees.

Children's blood lead levels differed significantly between the exposed and control groups. Fifty-three percent of the employees' children had blood lead levels greater than 30 µg/dl, while no child in the control population had a value greater than 30 µg/dl. The mean blood lead for the children of the employees was 49.2 µg/dl with a standard deviation of 8.3 µg/dl. These data represent the population average for yearly individual average levels. The employees had an average greater than 60 µg/dl. Still, this is lower than the industry average. Of the eight children with blood levels greater than 40 µg/dl, seven had fathers with blood lead greater than 50 µg/dl. Yet there was not a significant correlation between children's blood lead level and father's blood lead level.

Investigations were made into the possibility that other lead exposures could account for the observed difference in blood lead levels between children of employees and control children. In 11 of the 33 pairs finally included in the study, potential lead exposures other than fathers' occupations were found in the employee child of the matched pair. These included a variety of lead sources such as automobile body painting, casting of lead, and playing with spent shell casings. The control and exposed populations were again compared after removing these 11 pairs from consideration. There was still a statistically significant difference in blood lead level between the two groups of children.

An examination of personal hygiene practices of the workers showed that within high exposure category jobs, greater compliance with recommended lead containment practices resulted in lower mean blood lead levels in children. Mean blood leads were 17.3, 36.0 and 41.9 µg/dl for good, moderately good and poor compliance groups, respectively. In fact, there was only a small difference between the good hygiene group within the high exposure category and the mean of the control group (17.3 µg/dl vs. 15.9 µg/dl). Insufficient sample sizes were available to evaluate the effect of compliance on medium and low lead exposures for fathers.

Dolcourt et al. (1978) investigated lead absorption in children of workers in a plant that manufactures lead-acid storage batteries. The plant became known to these researchers as a result of finding an elevated blood lead level in a 20-month-old child during routine

screening. Although the child was asymptomatic, his mother proved not to be. Two siblings were also found to have elevated blood lead levels. The mother was employed by the plant; her work involved much hard labor and brought her into continual contact with powdery lead oxide. No uniforms or garment covers were provided by the company. As a result of these findings, screening was offered to all children of plant employees.

During February to May 1977, 92 percent of 63 eligible children appeared for screening. Age ranged from 10 months to 15 years. About equal numbers of girls and boys underwent screening. Fingerstick blood samples were collected on filter paper and were analyzed for lead by AAS. Children with blood lead levels equal to or greater than 40 µg/dl were referred for more detailed medical evaluation including an analysis of a venous blood specimen for lead. Dust samples were collected from carpeting in each home and analyzed for lead by graphite furnace AAS. Home tap water was analyzed for lead by AAS, and house paint was analyzed for lead by XRF.

Of the 58 children who had the initial fingerstick blood lead elevation, 69 percent had blood lead levels equal to or greater than 30 µg/dl. Ten children from six families had blood lead levels equal to or greater than 40 µg/dl, and blood lead levels were found to vary markedly with age. The 0- to 3-year old category exhibited the highest mean with the 3- to 6-year-olds the next highest (39.2 µg/dl). Lowest mean values were found in the equal to or greater than 10-year-old group (26.7 µg/dl).

More detailed investigation of the six families with the highest blood lead levels in their children revealed the following: five of the six lived in rural communities, with no pre-existing source of lead from water supply, house paint, industrial emissions or heavy automobile traffic. However, dust samples from the carpets exhibited excessively high lead concentrations. These ranged from 1700 to 84,050 µg/g.

Fergusson et al. (1981) sampled three population groups: general population, employees of a battery plant, and children of battery plant employees, using hair lead levels as indices of lead. Hair lead levels ranged from 1.2 to 110.9 µg/g in the 203 samples from the general population. The distribution of hair lead levels was nearly lognormal. Employees of the battery factory had the highest hair lead levels (median ~250 µg/g) while family members (median ~40 µg/g) had a lesser degree of contamination and the general population (median ~5 µg/g) still less.

Analysis of variance results indicated a highly significant difference between mean lead levels of the general survey and family members of the employees, and a significant difference between the mean lead levels in the hair of the employees and their families. No significant differences were found comparing mean hair lead levels among family members in terms of age and sex. The analyses of the house dust suggested that the mechanism of exposure of family

members is via the lead in dust that is carried home. Mean dust lead levels among the homes of factory employees was 5580 µg/g while the dust inside of houses along a busy road was only 1620 µg/g. Both of these concentrations are for particles less than 0.1 mm.

Dolcourt et al. (1981) reported two interesting cases of familiar exposure to lead caused by recycling of automobile storage batteries. The first case was of a 22 member, 4 generation family living in a three bedroom house in rural eastern North Carolina. The great grandfather of the index case worked at a battery recycling plant. He had two truckloads of spent casings delivered to the home to serve as fuel for the wood stove; the casings were burned over a 3-month period.

The index case presented with classic signs of acute lead encephalopathy, the most severe and potentially fatal form of acute lead poisoning. The blood lead level was found to be 220 µg/dl. Three months after initial diagnosis and after chelation therapy, she continued to have seizures and was profoundly mentally retarded. Dust samples were obtained by vacuum cleaner and analyzed for lead by flameless AAS. Dust from a sofa near the wood stove contained 13,283 µg/g lead while the kitchen floor dust had 41,283 µg/g. There was no paint lead. All other members of the family had elevated blood lead levels ranging from 27-256 µg/dl.

The other case involved a truck driver working in a low exposure area of a battery recycling operation in rural western North Carolina. He was operating an illegal battery recycling operation in his home by melting down reclaimed lead on the kitchen stove. No family member was symptomatic for lead symptoms but blood lead levels ranged from 24 to 72 µg/dl. Soil samples taken from the driveway, which was paved with fragments of the discarded battery casing, contained 12-13 percent lead by weight.

In addition to families being exposed as a result of employment at battery plants, studies have been reported recently for smelter worker families (Rice et al., 1978; Snee, 1982c). Rice et al. studied lead contamination in the homes of secondary lead smelters. Homes of employees of secondary smelters in two separate geographic areas of the country were examined to determine whether those homes had a greater degree of lead contamination than homes of workers in the same area not exposed to lead. Both sets of homes (area I and II) were examined at the same time of the year.

Thirty-three homes of secondary smelter employees were studied; 19 homes in the same or similar neighborhoods were studied as controls. Homes studied were in good condition and were one or two family dwellings. Blood lead levels were not obtained for children in these homes. In the homes of controls, a detailed occupational history was obtained for each employed person. Homes where one or more residents were employed in a lead contaminated environment were excluded from the analysis.

House dust samples were collected by Vostal's method and were analyzed for lead by AAS. In one of the areas, samples of settled dust were collected from the homes of employees and controls. Dust was collected over the doorways. In homes where the settled dust was collected, zinc protoporphyrin (ZPP) determinations were made in family members of the lead workers and in the controls.

In both areas the wipe samples were statistically significantly higher in the homes of employees compared to controls (geometric mean 79.3 ± 61.8 μg/g vs. 28.8 ± 7.4 μg/g Area I; 112.0 ± 2.8 μg/g vs. 9.7 ± 3.9 μg Area II). No significant differences were found between workers' homes or controls between Area I and Area II. Settled dust lead was significantly higher in the homes of employees compared to controls (3300 vs. 1200 μg/g). Lead content of particulate matter collected at the curb and of paint chips collected in the home was not significantly different between employee homes and controls. Zinc protoporphyrin determinations were done on 15 children, 6 years or younger. ZPP levels were higher in employee children than in control children. Mean levels were 61.4 μg/ml and 37.6 μg/ml, respectively.

It should be noted again that the wipe samples were not different between employee homes in the two areas. Interviews with employees indicated that work practices were quite similar in the two areas. Most workers showered and changed before going home. Work clothes were washed by the company. Obviously much closer attention needs to be paid to other potential sources of lead introduction into the home (e.g., automobile surfaces).

11.5.6 Miscellaneous Studies

11.5.6.1 Studies Using Indirect Measures of Air Exposure.

11.5.6.1.1 Studies in the United States. A 1973 Houston study examined the blood lead levels of parking garage attendants, traffic policemen, and adult females living near freeways (Johnson et al., 1974). A control group for each of the three exposed populations was selected by matching for age, education and race. Unfortunately, the matching was not altogether successful; traffic policemen had less education than their controls, and the garage employees were younger than their controls. Females were matched adequately, however. It should be noted that the mean blood lead values for traffic policemen and parking garage attendants, two groups regularly exposed to higher concentrations of automotive exhausts, were significantly higher than the means for their relevant control groups. Statistically significant differences in mean values were not found, however, between women living near a freeway, and control women living at greater distances from the freeway.

A study of the effects of lower level urban traffic densities on blood lead levels was undertaken in Dallas, Texas, in 1976 (Johnson et al., 1978). The study consisted of two phases. One phase measured air lead values for selected traffic densities and conditions, ranging from equal to or less than 1,000 to about 37,000 cars/day. The second phase consisted of an epidemiological study of traffic density and blood lead levels among residents. Figure 11-30 shows the relationship between arithmetic means of air lead and traffic density. As can be seen from the graph, a reasonable fit was obtained.

In addition, for all distances measured (1.5 to 30.5 m from the road), air lead concentrations declined rapidly with distance from the street. At 15 m, concentrations were about 55 percent of the street concentrations. In air lead collections from 1.5 to 30.5 m from the street, approximately 50 percent of the airborne lead was in the respirable range (<1 μm), and the proportions in each size class remained approximately the same as the distance from the street increased.

Soil lead concentrations were higher in areas with greater traffic density, ranging from 73.6 μg/g at less than 1,000 cars per day to a mean of 105.9 at greater than 19,500 cars per day. The maximum soil level obtained was 730 μg/g.

Dustfall samples for 28 days from 9 locations showed no relationship to traffic densities, but outdoor levels were at least 10 times the indoor concentration in nearby residences.

In the second phase, three groups of subjects, 1- to 6-years-old, 18- to 49-years old and 50 years and older, were selected in each of four study areas. Traffic densities selected were less than 1,000, 8,000 to 14,000, 14,000 to 20,000 and 20,000 to 25,000 cars/day. The study groups averaged about 35 subjects, although the number varied from 21 to 50. The smallest groups were from the highest traffic density area. No relationship between traffic density and blood lead levels in any of the age groups was found (Figure 11-31). Blood lead levels were significantly higher in children, 12 to 18 μg/dl, than in adults, 9 to 14 μg/dl.

Caprio et al. (1974) compared blood lead levels and proximity to major traffic arteries in a study reported in 1971 that included 5226 children in Newark, New Jersey. Over 57 percent of the children living within 30.5 m of roadways had blood lead levels greater than 40 μg/dl. For those living between 30.5 and 61 m from the roadways, more than 27 percent had such levels, and at distances greater than 61 m, 31 percent exceeded 40 μg/dl. The effect of automobile traffic was seen only in the group that lived within 30.5 m of the road.

No other sources of lead were considered in this study. However, data from other studies on mobile sources indicate that it is unlikely that the blood lead levels observed in this study resulted entirely from automotive exhaust emissions.

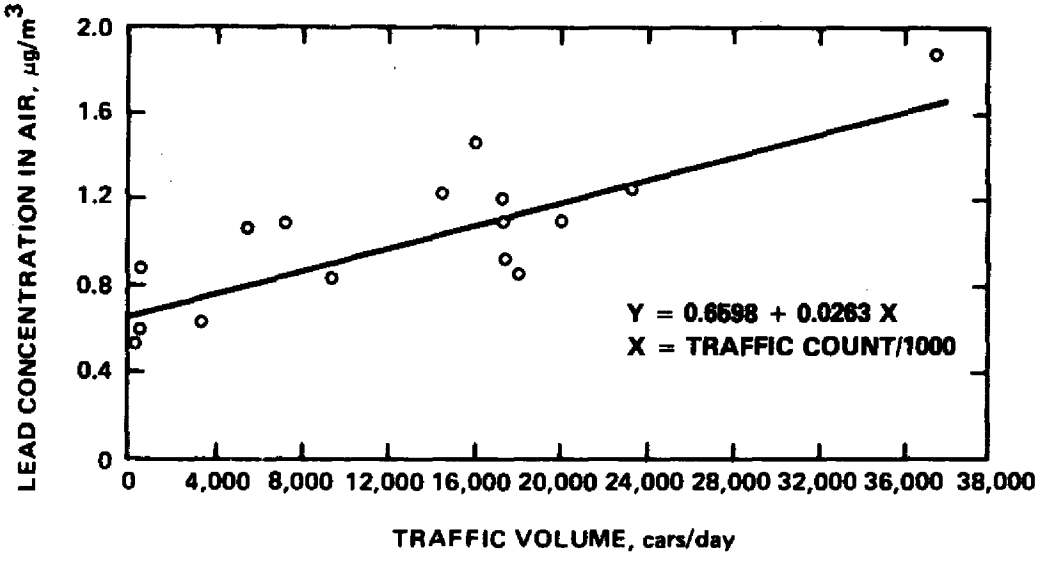

Figure 11-30. Arithmetic mean of air lead levels by traffic volume, Dallas, 1976.

In 1964, Thomas et al. (1967) investigated blood lead levels in 50 adults who had lived for at least 3 years within 76 m of a freeway (Los Angeles) and those of 50 others who had lived for a similar period near the ocean or at least 1.6 km from a freeway. Mean blood lead levels for those near the freeway were 22.7 ± 5.6 for men and 16.7 ± 7.0 μg/dl for women. These concentrations were higher than for control subjects living near the ocean: 16.0 ± 8.4 μg/dl for men and 9.9 ± 4.9 μg/dl for women. The higher values, however, were similar to those of other Los Angeles populations. Measured mean air concentrations of lead in Los Angeles for October 1964 were 12.25 ± 2.70 $\mu g/m^3$ at a location 9 m from the San Bernardino freeway; 13.25 ± 1.90 $\mu g/m^3$ at a fourth floor location 91.5 m from the freeway; and 4.60 ± 1.92 $\mu g/m^3$ 1.6 km from the nearest freeway. The investigators concluded that the differences observed were consistent with coastal inland atmospheric and blood lead gradients in the Los Angeles basin and that the effect of residential proximity to a freeway (7.6 to 76 m) was not demonstrated.

Ter Haar and Chadzynski report a study of blood lead levels of children living near three heavily travelled streets in Detroit (Ter Haar, 1981; Ter Haar and Chadzynski, 1979). Blood lead levels were not found to be related to distance from the road but were related to conditions of housing and age of the child after multiple regression analyses.

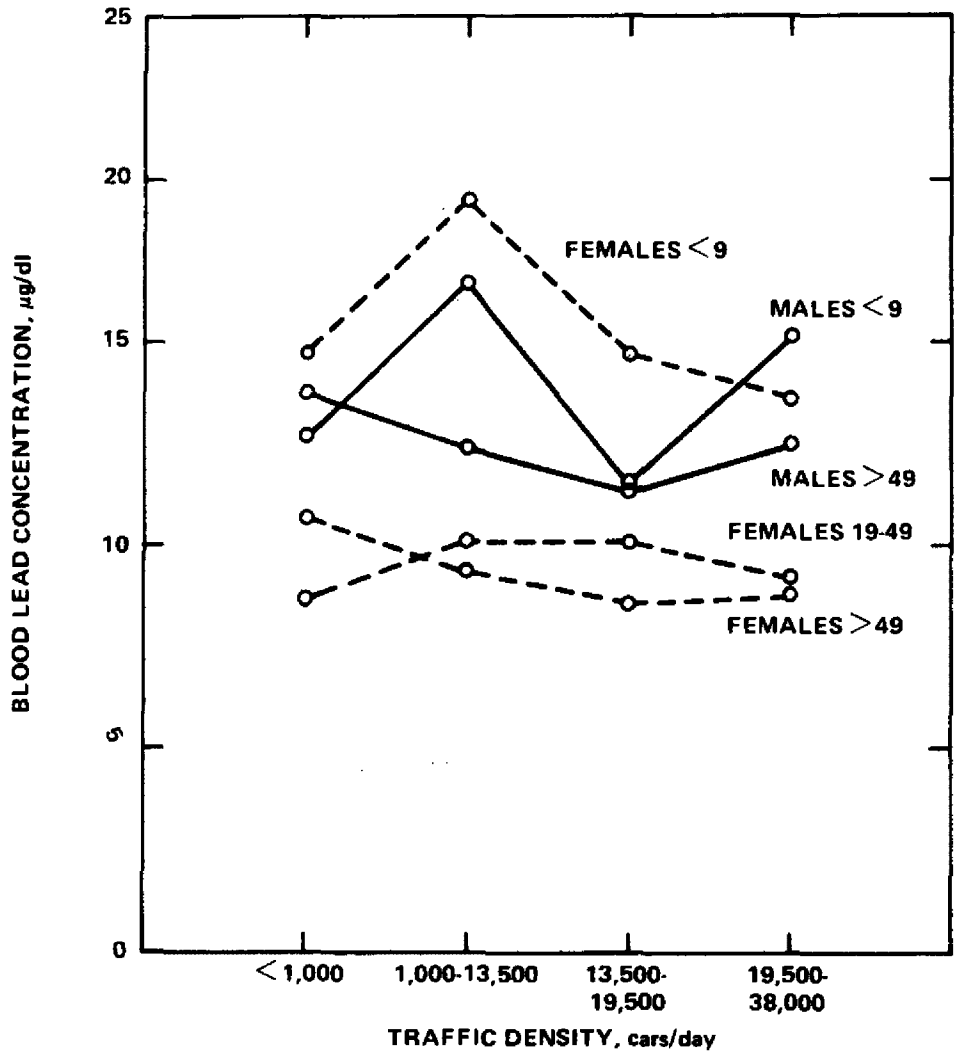

Figure 11-31. Blood lead concentration and traffic density by sex and age, Dallas, 1976.

11.5.6.1.2 British Studies. In a Birmingham, England study, mean blood lead levels in 41 males and 58 females living within 800 m of a highway interchange were 14.41 and 10.93 µg/dl, respectively, just before the opening of the interchange in May 1972 (Waldron, 1975). From October 1972 to February 1973, the respective values for the same individuals were 18.95 and 14.93 µg/dl. In October 1973 they were 23.73 and 19.21 µg/dl. The investigators noted difficulties in the blood collection method during the baseline period and changed from capillary to venous blood collection for the remaining two samples. To interpret the significance of the change in blood collection method, some individuals gave both capillary and venous blood at the second collection. The means for both capillary and venous bloods were calculated for the 18 males and 23 females who gave both types of blood samples (Barry, 1975). The venous blood mean values for both these males and females were lower by 0.8 and 0.7 µg/dl, respectively. If these differences were applied to the means of the third series, the mean for males would be reduced to 24.8 µg/dl and that for the females to 18.7 µg/dl. These adjusted means still show an increase over the means obtained for the first series. Comparing only the means for venous bloods, namely series two and three, again shows an increase for both groups. The increase in blood lead values was larger than expected following the model of Knelson et al. (1973), because air lead values near the road were approximately 1 µg/m^3. The investigators concluded that either the lead aerosol of very small particles behaved more like a gas so that considerably more than 37 percent of inhaled material was absorbed or that ingestion of lead contaminated dust might be responsible.

Studies of taxicab drivers have employed different variables to represent the drivers' lead exposure (Flindt et al., 1976; Jones et al., 1972): one variable was night vs. dayshift drivers (Jones et al., 1972); the other, mileage driven (Flindt et al., 1976). No difference was observed, in either case.

The studies reviewed show that automobiles produce sufficient emissions to increase air and nearby soil concentrations of lead as well, as increase blood lead concentrations in children and adults. The problem is of greater importance when houses are located within 100 ft (30 m) of the roadway.

11.5.6.2 Miscellaneous Sources of Lead. The habit of cigarette smoking is a source of lead exposure. Shaper et al. (1982) report that blood lead concentration is higher for smokers than nonsmokers and that cigarette smoking makes a significant independent contribution to blood lead concentration in middle-aged men in British towns. A direct increase in lead intake from cigarettes is thought to be responsible. Hopper and Mathews (1983) comment that current smoking has a significant effect on blood lead level, with an average increase of 5.8 percent in blood lead levels for every 10 cigarettes smoked per day. They also report that

past smoking history had no measurable effect on blood lead levels. Hasselblad and Nelson (1975) report an average increase in women's blood lead levels of 1.3 µg/dl in the study of Tepper and Levin (1975).

Although no studies are available, it is conceivable that destruction of lead-containing plastics (to recover copper), which has caused cattle poisoning, also could become a source of lead exposure for humans. Waste disposal is a more general problem because lead-containing materials may be incinerated and may thus contribute to increased air lead levels. This source of lead has not been studied in detail. Tyrer (1977) cautions of the lead hazard in the recycling of waste.

The consumption of illicitly distilled liquor has been shown to produce clinical cases of lead poisoning. Domestic and imported earthenware (De Rosa et al., 1980) with improperly fired glazes have also been related to clinical lead poisoning. This source becomes important when foods or beverages high in acid are stored in earthenware containers, because the acid releases lead from the walls of the containers.

Particular cosmetics, popular among some Oriental and Indian ethnic groups, contain high percentages of lead that sometimes are absorbed by users in quantities sufficient to be toxic. Ali et al. (1978) and Attenburrow et al. (1980) discuss the practice of surma and lead poisoning. Other sources of lead are presented in Table 11-60.

TABLE 11-60. SOURCES OF LEAD

Source	References
Gasoline Sniffing	Kaufman and Wiese (1978) Coodin and Boeckx (1978) Hansen and Sharp (1978)
Colored Gift Wrapping	Bertagnolli and Katz (1979)
Gunshot Wound	Dillman et al. (1979)
Drinking Glass Decorations	Anonymous (1979)
Electric Kettles	Wigle and Charlebois (1978)
Hair dye	Searle and Harnden (1979)
Snuff use	Filippini and Simmler (1980)
Firing ranges	Fischbein et al. (1979, 1980b)

11.6 SUMMARY AND CONCLUSIONS

Studies of ancient populations using bone and teeth show that levels of internal exposure of lead today are substantially elevated over past levels. Studies of current populations living in remote areas far from urbanized cultures show blood lead levels in the range of 1 to 5 μg/dl. In contrast to the blood lead levels found in remote populations, data from current U.S. populations have geometric means ranging from 10 to 20 μg/dl depending on age, race, sex and degree of urbanization. These higher current exposure levels appear to be associated with industrialization and widespread commercial use of lead, e.g. in gasoline combustion.

Age appears to be one of the single most important demographic covariates of blood lead levels. Blood lead levels in children up to six years of age are generally higher than those in non-occupationally exposed adults. Children aged two to three years tend to have the highest levels as shown in Figure 11-32. Blood lead levels in non-occupationally exposed adults may increase slightly with age due to skeletal lead accumulation.

Sex has a differential impact on blood lead levels depending on age. No significant differences exist between males and females less than seven years of age. Males above the age of seven generally have higher blood lead levels than females.

Race also plays a role, in that blacks generally have higher blood lead levels than either whites or Hispanics and urban black children (aged 6 mo. to 5 yr.) have markedly higher blood lead concentrations than any other racial or age group. Possible genetic factors associated with race have yet to be fully disentangled from differential exposure levels as important determinants of blood lead levels.

Blood lead levels also generally increase with degree of urbanization. Data from NHANES II show blood lead levels in the United States, averaged from 1976 to 1980, increasing from a geometric mean of 11.9 μg/dl in rural populations to 12.8 μg/dl in urban populations less than one million, increasing again to 14.0 μg/dl in urban populations of one million or more.

Recent U.S. blood lead levels show a downward trend occurring consistently across race, age and geographic location. The downward pattern commenced in the early part of the 1970's and has continued into 1980. The downward trend has occurred from a shift in the entire distribution and not through a truncation in the high blood lead levels. This consistency suggests a general causative factor, and attempts have been made to identify the causative element. Reduction in lead emitted from the combustion of leaded gasoline is a prime suspect, but at present no causal relationship has been established.

Blood lead levels, examined on a population basis, have similarly skewed distributions. Blood lead levels, from a population thought to be homogenous in terms of demographic and lead exposure characteristics, approximately follow a lognormal distribution. The geometric standard deviations, an estimation of dispersion, for four different studies are shown in Table 11-61. The values, including analytic error, are about 1.4 for children and possibly somewhat

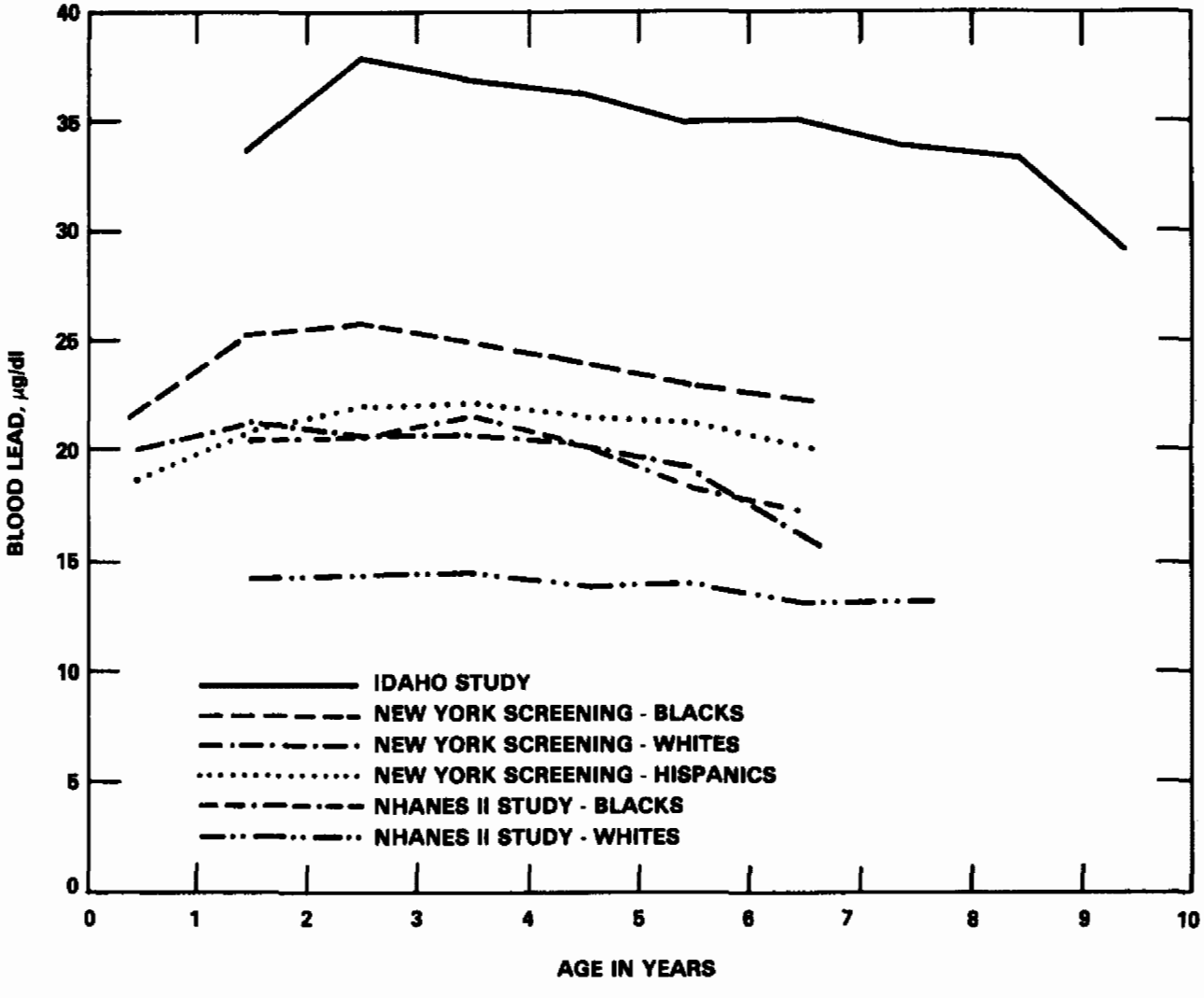

Figure 11-32. Geometric mean blood lead levels by race and age for younger children in the NHANES II study, and the Kellogg/Silver Valley and New York Childhood Screening Studies.

TABLE 11-61. SUMMARY OF POOLED GEOMETRIC STANDARD DEVIATIONS AND ESTIMATED ANALYTIC ERRORS

Study	Pooled Geometric Standard Deviations				Estimated Analytic Error
	Inner City Black Children	Inner City White Children	Adults Females	Adult Males	
NHANES II	1.37	1.39	1.36[a]	1.40[a]	0.021
N.Y. Childhood Screening Study	1.41	1.42	-	-	(b)
Tepper-Leven	-	-	1.30	-	0.056[c]
Azar et al.	-	-	-	1.29	0.042[c]

Note: To calculate an estimated person-to-person GSD, compute Exp $[((\ln(GSD))^2 - \text{Analytic Error})^{1/2}]$

[a]pooled across areas of differing urbanization

[b]not known, assumed to be similar to NHANES II

[c]taken from Lucas (1981).

smaller for adults. This allows an estimation of the upper tail of the blood lead distribution, the group at higher risk.

Because the main purpose of this chapter is to examine relationships of lead in air and lead in blood under ambient conditions, the results of studies most appropriate to this area have been emphasized. A summary of the most appropriate studies appears in Table 11-62. At air lead exposures of 3.2 $\mu g/m^3$ or less, there is no statistically significant difference between curvilinear and linear blood lead inhalation relationships. At air lead exposures of 10 $\mu g/m^3$ or more, either nonlinear or linear relationships can be fitted. Thus, a reasonably consistent picture emerges in which the blood-lead air-lead relationship by direct inhalation was approximately linear in the range of normal ambient exposures of 0.1 - 2.0 $\mu g/m^3$ (as discussed in Chapter 7). Differences among individuals in a given study (and among several studies) are large, so that pooled estimates of the blood lead inhalation slope depend upon the the weight given to various studies. Several studies were selected for analysis, based upon factors described earlier. EPA analyses* of experimental and clinical studies (Griffin et al. 1975; Rabinowitz et al., 1974, 1976, 1977; Kehoe 1961a,b,c; Gross 1981; Hammond et al., 1981) suggest that blood lead in adults increases by 1.64 ± 0.22 µg/dl from direct inhalation

*Note: The term EPA analyses refers to calculations done at EPA. A brief discussion of the methods used is contained in Appendix 11-B; more detailed information is available at EPA upon request.

TABLE 11-62. SUMMARY OF BLOOD INHALATION SLOPES, (β)
μg/dl per μg/m^3

Population	Study	Study Type	N	(β) Slope μg/dl per μg/m^3	Model Sensitivity Of Slope*
Children	Angle and McIntire, 1979 Omaha, NE	Population	1074	1.92	(1.40 - 4.40)[1,2,3]
	Roels et al. (1980) Belgium	Population	148	2.46	(1.55 - 2.46)[1,2]
	Yankel et al. (1977); Walter et al. (1980) Idaho	Population	879	1.52	(1.07 - 1.52)[1,2,3]
Adult Males	Azar et al. (1975). Five groups	Population	149	1.32	(1.08 - 2.39)[2,3]
	Griffin et al. (1975), NY prisoners	Experiment	43	1.75	(1.52 - 3.38)[4]
	Gross (1979)	Experiment	6	1.25	(1.25 - 1.55)[2]
	Rabinowitz et al. (1973,1976, 1977)	Experiment	5	2.14	(2.14 - 3.51)[5]

*Selected from among the most plausible statistically equivalent models. For nonlinear models, slope at 1.0 μg/m^3.

[1]Sensitive to choice of other correlated predictors such as dust and soil lead.

[2]Sensitive to linear vs. nonlinear at low air lead.

[3]Sensitive to age as a covariate.

[4]Sensitive to baseline changes in controls.

[5]Sensitive to assumed air lead exposure.

of each additional $\mu g/m^3$ of air lead. EPA analyses of population studies (Yankel et al., 1977; Roels et al., 1980; Angle and McIntire, 1979) suggest that, for children, the blood lead increase is 1.97 ± 0.39 μg/dl per $\mu g/m^3$ for air lead. EPA anaylsis of Azar's population study (Azar et al., 1975) yields a slope of 1.32 ± 0.38 for adult males.

These slope estimates are based on the assumption that an equilibrium level of blood lead is achieved within a few months after exposure begins. This is only approximately true, since lead stored in the skeleton may return to blood after some years. Chamberlain et al. (1978) suggest that long term inhalation slopes should be about 30 percent larger than these estimates. Inhalation slopes quoted here are associated with a half-life of blood lead in adults of about 30 days. O'Flaherty et al. (1982) suggest that the blood-lead half-life may increase slightly with duration of exposure, but this has not been confirmed (Kang et al., 1983).

One possible approach would be to regard all inhalation slope studies as equally informative and to calculate an average slope using reciprocal squared standard error estimates as weights. This approach has been rejected for two reasons. First, the standard error estimates characterize only the internal precision of an estimated slope, not its representativeness (i.e., bias) or predictive validity. Secondly, experimental and clinical studies obtain more information from a single individual than do population studies. Thus, it may not be appropriate to combine the two types of studies.

Estimates of the inhalation slope for children are only available from population studies. The importance of dust ingestion as a non-inhalation pathway for children is established by many studies. A slope estimate has been derived for air lead inhalation based on those studies (Angle and McIntire 1979; Roels et al., 1980; Yankel et al., 1977) from which the air inhalation and dust ingestion contributions can both be estimated.

While direct inhalation of air lead is stressed, this is not the only air lead contribution that needs to be considered. Smelter studies allow partial assessment of the air lead contributions to soil, dust and finger lead. Conceptual models allow preliminary estimation of the propagation of lead through the total food chain as shown in Chapter 7. Useful mathematical models to quantify the propagation of lead through the food chain need to be developed. The direct inhalation relationship does provide useful information on changes in blood lead as responses to changes in air lead on a time scale of several months. The indirect pathways through dust and soil and through the food chain may thus delay the total blood lead response to changes in air lead, perhaps by one or more years. The Italian ILE study facilitates partial assessment of this delayed response from leaded gasoline as a source.

Dietary absorption of lead varies greatly from one person to another and depends on the physical and chemical form of the carrier, on nutritional status, and on whether lead is

ingested with food or between meals. These distinctions are particularly important for consumption by children of leaded paint, dust and soil. Typical values of 10 percent absorption of ingested lead into blood have been assumed for adults and 25 to 50 percent for children.

It is difficult to obtain accurate dose-response relationships between blood lead levels and lead levels in food or water. Dietary intake must be estimated by duplicate diets or fecal lead determinations. Water lead levels can be determined with some accuracy, but the varying amounts of water consumed by different individuals adds to the uncertainty of the estimated relationships.

Quantitative analyses relating blood lead levels and dietary lead exposures have been reported. Studies on infants provide estimates that are in close agreement. Only one individual study is available for adults (Sherlock et al. 1982); another estimate from a number of pooled studies is also available. These two estimates are in good agreement. Most of the subjects in the Sherlock et al. (1982) and United Kingdom Central Directorate on Environmental Pollution (1982) studies received quite high dietary lead levels (>300 μg/day). The fitted cube root equations give high slopes at lower dietary lead levels. On the other hand, the linear slope of the United Kingdom Central Directorate on Environmental Pollution (1982) study is probably an underestimate of the slope at lower dietary lead levels. For these reasons, the Ryu et al. (1983) study is the most believable, although it only applies to infants. Estimates for adults should be taken from the experimental studies or calculated from assumed absorption and half-life values. Most of the dietary intake supplements were so high that many of the subjects had blood lead concentrations much in excess of 30 $\mu g/m^3$ for a considerable part of the experiment. Blood lead levels thus may not completely reflect lead exposure, due to the previously noted nonlinearity of blood lead response at high exposures. The slope estimates for adult dietary intake are about 0.02 μg/dl increase in blood lead per μg/day intake, but consideration of blood lead kinetics may increase this value to about 0.04. Such values are a bit lower than slopes of about 0.05 μg/dl per μg/day estimated from the population studies extrapolated to typical dietary intakes. The value for infants is larger.

The relation between blood lead and water lead is not clearly defined and is often described as nonlinear. Water lead intake varies greatly from one person to another. It has been assumed that children can absorb 25 to 50 percent of lead in water. Many authors chose to fit cube root models to their data, although polynomial and logarithmic models were also used. Unfortunately, the form of the model greatly influences the estimated contributions to blood leads from relatively low water lead concentration.

Although there is close agreement in the quantitative analyses of the relationship between blood lead level and dietary lead, there is a larger degree of variability in results of the various water lead studies. The relationship is curvilinear, but its exact form is yet to be determined. At typical levels for U.S. populations, the relationship appears linear. The

only study that determines the relationship based on lower water lead values (<100 µg/l) is the Pocock et al. (1983) study. The data from this study, as well as the authors themselves, suggest that in this lower range of water lead levels, the relationship is linear. Furthermore, the estimated contributions to blood lead levels from this study are quite consistent with the polynomial models from other studies. For these reasons, the Pocock et al. (1983) slope of 0.06 is considered to represent the best estimate. The possibility still exists, however, that the higher estimates of the other studies may be correct in certain situations, especially at higher water lead levels (>100 µg/l).

Studies relating soil lead to blood lead levels are difficult to compare. The relationship obviously depends on depth of soil lead, age of the children, sampling method, cleanliness of the home, mouthing activities of the children, and possibly many other factors. Various soil sampling methods and sampling depths have been used over time, and as such they may not be directly comparable and may produce a dilution effect of the major lead concentration contribution from dust which is located primarily in the top 2 cm of the soil. Increases in soil dust lead significantly increase blood lead in children. From several studies (Yankel et al., 1977; Angle and McIntire, 1979) EPA estimates an increase of 0.6 to 6.8 µg/dl in blood lead for each increase of 1000 µg/g in soil lead concentration. Values of about 2.0 µg/dl per 1,000 µg/g soil lead from the Stark et al. (1982) study may represent a reasonable median estimate. The relationship of housedust lead to blood lead is difficult to obtain. Household dust also increases blood lead, children from the cleanest homes in the Silver Valley/ Kellogg Study having 6 µg/dl less lead in blood, on average, than those from the households with the most dust.

A number of specific environmental sources of airborne lead have been evaluated for potential direct influence on blood lead levels. Combustion of leaded gasoline appears to be the largest contributor to airborne lead. Two studies used isotope ratios of lead to estimate the relative proportion of lead in the blood coming from airborne lead. From one study, by Manton, it can be estimated that between 7 and 41 percent of the blood lead in study subjects in Dallas resulted from airborne lead. Additionally, these data provide a means of estimating the indirect contribution of air lead to blood lead. By one estimate, only 10 to 20 percent of the total airborne contribution in Dallas is from direct inhalation.

From the ILE data in Facchetti and Geiss (1982), as shown in Table 11-63, the direct inhalation of air lead may account for 54 percent of the total adult blood lead uptake from leaded gasoline in a large urban center, but inhalation is a much less important pathway in suburban parts of the region (17 percent of the total gasoline lead contribution) and in the rural parts of the region (8 percent of the total gasoline lead contribution). EPA analyses of the preliminary results from the ILE study separated the inhalation and non-inhalation contributions of leaded gasoline to blood lead into the following three parts: (1) An increase

of about 1.7 μg/dl in blood lead per $\mu g/m^3$ of air lead, attributable to direct inhalation of the combustion products of leaded gasoline; (2) a sex difference of about 2 μg/dl attributable to lower exposure of women to indirect (non-inhalation) pathways for gasoline lead; and (3) a non-inhalation background attributable to indirect gasoline lead pathways, such as ingestion of dust and food, increasing from about 2 μg/dl in Turin to 3 μg/dl in remote rural areas. The non-inhalation background represents only two to three years of environmental accumulation at the new experimental lead isotope ratio. It is not clear how to extrapolate numerically these estimates to U.S. subpopulations; but it is evident that even in rural and suburban parts of a metropolitan area, the indirect (non-inhalation) pathways for exposure to leaded gasoline make a significant contribution to blood lead. This can be seen in Table 11-63. It should also be noted that the blood lead isotope ratio responded fairly rapidly when the lead isotope ratio returned to its pre-experimental value, but it is not yet possible to estimate the long term change in blood lead attributable to persistent exposures to accumulated environmental lead.

Studies of data from blood lead screening programs suggest that the downward trend in blood lead levels noted earlier is due to the reduction in air lead levels, which has been attributed to the reduction of lead in gasoline.

TABLE 11-63. ESTIMATED CONTRIBUTION OF LEADED GASOLINE TO BLOOD LEAD BY INHALATION AND NON-INHALATION PATHWAYS

Location	Air Lead Fraction From Gasoline(a)	Blood Lead Fraction From Gasoline(b)	Blood Pb From Gasoline In Air(c) μg/dl	Blood Lead Not Inhaled From Gasoline(d) μg/dl	Estimate Fraction Gas-Lead Inhalation(e)
Turin	0.873	0.237	2.79	2.37	0.54
<25 km	0.587	0.125	0.53	2.60	0.17
>25 km	0.587	0.110	0.28	3.22	0:08

(a) Fraction of air lead in Phase 2 attributable to lead in gasoline.
(b) Mean fraction of blood lead in Phase 2 attributable to lead in gasoline.
(c) Estimated blood lead from gas inhalation = β x (a) x (b), β = 1.6.
(d) Estimated blood lead from gas, non-inhalation = (f)-(e)
(e) Fraction of blood lead uptake from gasoline attributable to direct inhalation = (f)/(e)

Source: Facchetti and Geiss (1982), pp. 52-56.

Primary lead smelters, secondary lead smelters and battery plants emit lead directly into the air and ultimately increase soil and dust lead concentrations in their vicinity. Adults, and especially children, have been shown to exhibit elevated blood lead levels when living close to these sources. Blood lead levels in these residents have been shown to be related to air, as well as to soil or dust exposures.

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APPENDIX 11A
COMPARTMENTAL ANALYSIS

Many authors have noted that under conditions of constant lead exposure, blood lead concentrations change from one level to another apparent equilibrium level over a period of several months. A mathematical model is helpful in estimating the new apparent equilibrium level even when the duration of the experiment is not sufficiently long for this equilibrium level to have been achieved. The model assumes that lead in the body is held in some number of homogeneous and well-mixed pools or compartments. The compartments have similar kinetic properties and may or may not correspond to identifiable organ systems. In a linear kinetic model it is assumed that the rate of change of the mass of lead in compartment i at time t, denoted $X_i(t)$, is a linear function of the mass of lead in each compartment. Denote the fractional rate of transfer of lead into compartment i from compartment j by K_{ij} (fraction per day), and let $I_i(t)$ be the total external lead input into compartment i at time t in units such as μg/day. The elimination rate from compartment i is denoted K_{0i}. The compartmental model is:

$$dX_i(t)/dt = I_i(t) + K_{i1} X_1(t) + \cdots + K_{in}X_n(t) - (K_{0i} + K_{1i} + \cdots + K_{ni})X_i(t)$$

for each of the n compartments. If the inputs are all constant, then each $X_i(t)$ is the sum of (at most) n exponential functions of time (see for example, Jacquez, 1972).

For the one-compartment model:

$$dX_i(t)/dt = I_1 - K_{01} X_1(t)$$

with an initial lead burden $X_1(0)$ at time 0,

$$X_1(t) = X_1(0) \exp(-K_{01}t) + [(I_1/K_{01}) (1-\exp(-K_{01}t)]$$

The mass of lead at equilibrium is I_1/K_{01} μg. We may think of this pool as "blood lead". If the pool has volume V_1 then the equilibrium concentration is $I_1/K_{01} V_1$ μg/dl. Intake from several pathways will have the form:

$$I_1 = A_1 \text{ (Pb-Air)} + A_2 \text{ (Pb-Diet)} + \cdots$$

so that the long term concentration is

$$I_1/K_{01} V_1 = (A_1/K_{01}V_1) \text{ Pb-Air} + \cdots$$

The inhalation coefficient is $\beta = A_1/K_{01}V_1$. The blood lead half-life is $0.693/K_{01}$.

Models with two or more compartments will still have equilibrium concentrations in blood and other compartments that are proportional to the total lead intake, and thus increase linearly with increasing concentrations in air, dust, and diet. The relationship between the exponential parameters and the fractional transfer coefficients will be much more complicated, however.

Models with two or three pools have been fitted by Rabinowitz et al. (1976, 1977) and by Batschelet et al. (1979). The pools are tentatively identified as mainly blood, soft tissue and bone. But as noted in Section 11.4.1.1, the "blood" pool is much larger than the volume of blood itself, and so it is convenient to think of this as the effective volume of distribution for pool 1. A five-pool model has been proposed by Bernard (1977), whose pools are mainly blood, liver, kidney, soft bones and hard bone.

The major conclusion of this Appendix is that linear kinetic mechanisms imply linear relationships between blood lead and lead concentrations in environmental media. Any extended discussion of nonlinear kinetic mechanisms is premature at this point, but it is of some interest that even simple nonlinear kinetic models produce plausible nonlinear blood lead vs. concentration relationships. For example, if the rate of blood lead excretion into urine or storage "permanently" in bone increases linearly with blood lead, then at high blood lead levels, blood increases only as the square root of lead intake. Let M denote the mass of lead in pool 1 at which excretion rate doubles. Then:

$$dX_1(t)/dt = I_1 - K_{01}(1 + X_1(t)/M_1)X_1(t)$$

has an equilibrium level:

$$X_1 = M_1(\sqrt{1 + 4I_1/K_{01}M_1} - 1)/2$$

This is approximately linear in intake I when I_1 is small, but a square root function of intake when it is large. Other plausible models can be constructed.

APPENDIX 11B
FITTING CURVES TO BLOOD LEAD DATA

The relationship between blood lead and the concentrations of lead in various environmental media is a principal concern of this chapter. It is generally accepted that the geometric mean blood lead is some function, f, of the concentration of air lead and of lead in diet, dust, soil and other media. It has been observed that blood lead levels have a highly skewed distribution even for populations with relatively homogeneous exposure, and that the variability in blood lead is roughly proportional to the geometric mean blood lead or to the arithmetic mean (constant coefficient of variation). Thus, instead of the usual model in which random variations are normally distributed, a model is assumed here in which the random deviations are multiplicative and lognormally distributed with geometric mean 1 and geometric standard deviation (GSD) e^{σ}. The model is written

$$\text{Pb-Blood} = f\ (\text{Pb-Air, etc.})\ e^{\sigma z}$$

where z is a random variable with mean 0 and standard deviation 1. It has a Gaussian or normal distribution. The model is fitted to data in logarithmic form

$$\ln(\text{Pb-Blood}) = \ln\ (f)$$

even when f is assumed to be a linear function, e.g.,

$$f = \beta\ \text{Pb-Air} + \beta_o + \beta_1\ \text{Pb-Dust} + \ldots$$

The nonlinear function, fitted by most authors (e.g., Snee, 1982b), is a power function with shape parameter λ,

$$f = (\beta\ \text{Pb-Air} + \beta_0 + \beta_1\ \text{Pb-Dust} + \ldots)^{\lambda}$$

These functions can all be fitted to data using nonlinear regression techniques. Even when the nonlinear shape parameter λ has a small statistical uncertainty or standard error associated with it, a highly variable data set may not clearly distinguish the linear function ($\lambda = 1$) from a nonlinear function ($\lambda \neq 1$). In particular, for the Azar data set, the residual sum of squares is shown as a function of the shape parameter λ, in Figure 11B-1. When only a

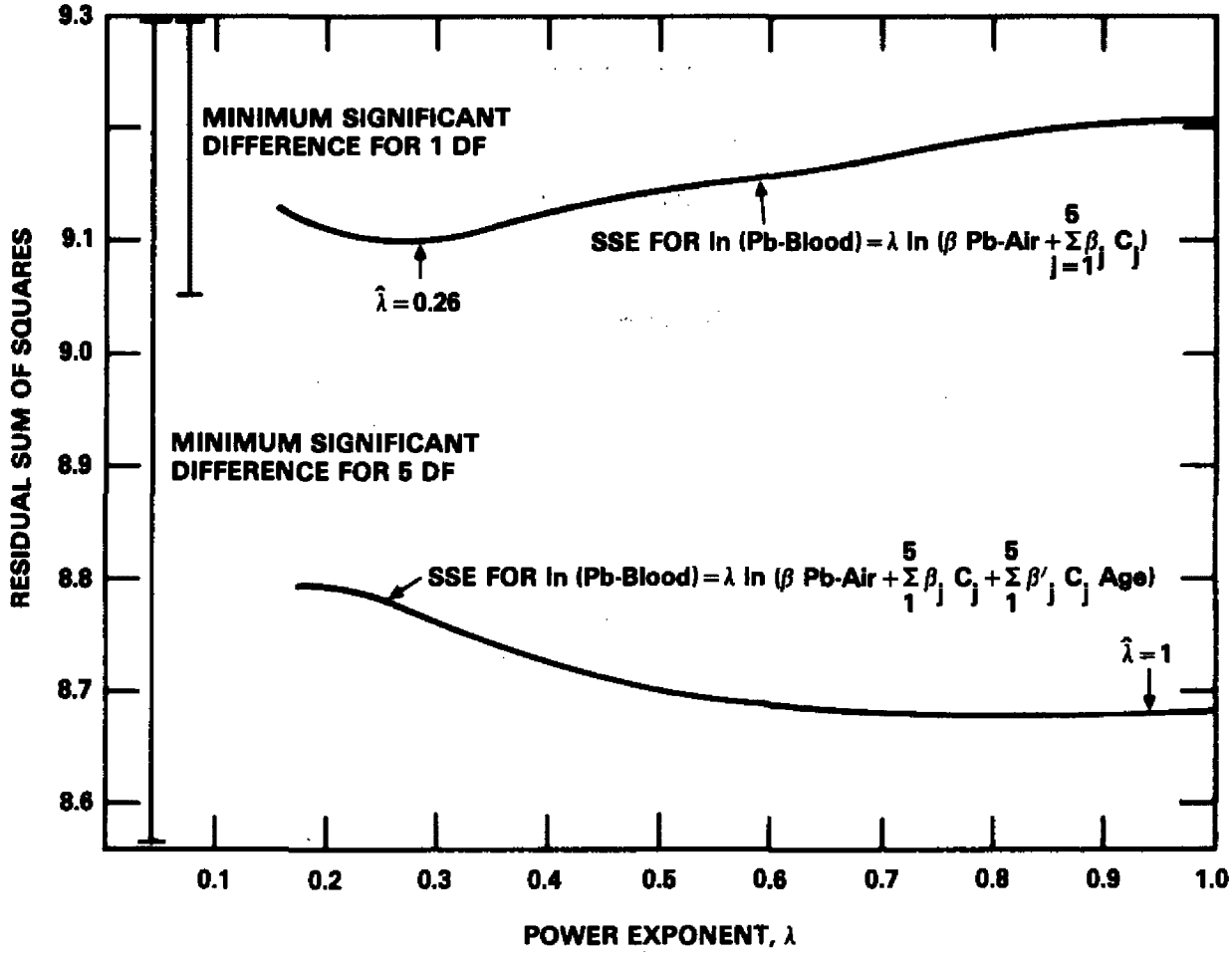

Figure 11 B-1. Residual sum of squares for nonlinear regression models for Azar data (N = 149).

separate intercept (background) is assumed for each subpopulation, the best choice is λ = 0 26; but when age is also used as a covariate for each subpopulation, then the linear model is better. However, the approximate size of the difference, in residual sum of squares required to decide at the 5 percent significance level that a nonlinear model is better (or worse) than a linear model, is larger than the observed difference in sum of squares for any λ>0.2 (Gallant, 1975). Therefore a linear model is used unless evidence of nonlinearity is very strong, as with some of Kehoe's studies and the Silver Valley/Kellogg study. Nonlinearity is detectable only when blood lead is high (much above 35 or 40 µg/dl), and intake is high, e.g., air lead much above 10 µg/m^3.. Additional research is needed on the relationship between lead levels and lead intake from all environmental pathways.

The "background" or intercept term β_0 in most models requires some comment. As the Manton and Italian lead isotope studies show, lead added to a regional environment by combustion of gasoline accumulates a large non-inhalation component even after only 2 years (see Figure 11-26). The non-inhalation contribution in the Turin region was nearly independent of location (air lead). It is not possible to assign causes, e.g., ingestion of food, dust, or water by adults, so no direct extrapolation to U.S. populations is possible at this time due to unknown differences in non-air exposures between the U.S. and Italy. It is probable that the non-inhalation contribution to blood lead increases with time as lead accumulates in the environment. After many years, one might obtain a figure like Figure 11B-2. Another concept is that such a curve should predict zero blood lead increase at zero air lead. If the blood lead curve is forced to pass through 0 when air lead = 0, a nonlinear curve is required. It has been concluded that a positive intercept term is needed to account for intake from accumulated lead in the environment, which precludes fully logarithmic models such as

$$\ln (\text{Pb-Blood}) = \ln (\beta_0) + \beta \ln (\text{Pb-Air}) + \beta_1 \ln (\text{Pb-Dust}) + \ldots$$

It must be acknowledged that such models may provide useful interpolations over a range of air lead levels; e.g., the Goldsmith-Hexter equation predicts blood lead 3.4 µg/dl at an air lead <0.004 µg/m^3 in the Nepalese subjects in Piomelli et al. (1980).

The final concern is that the intercept term may represent indirect sources of lead exposure that include previous air lead exposures. To the extent that present and previous air lead exposures are correlated, the intercept or background term may introduce apparent curvilinearities in the population studies of inhalation. The magnitude of this effect is unknown.

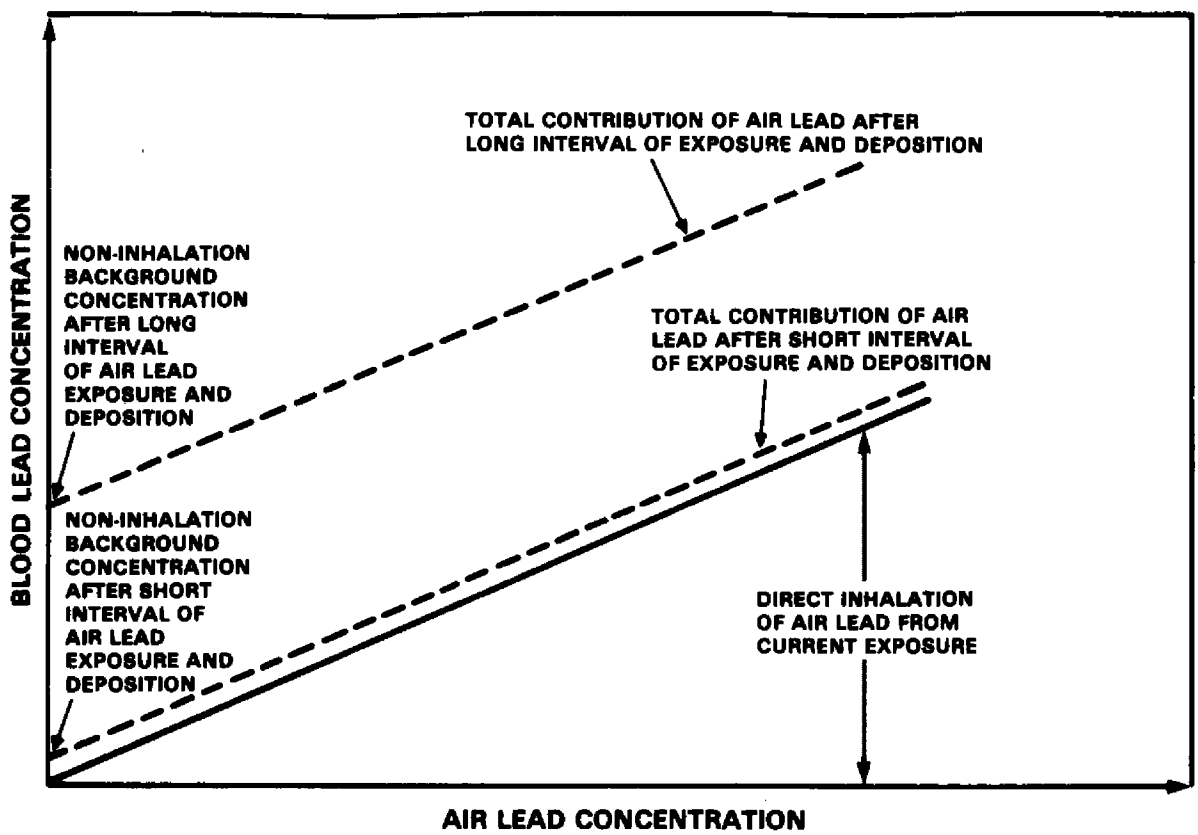

Figure 11 B-2. Hypothetical relationship between blood lead and air lead by inhalation and non-inhalation.

APPENDIX 11C
ESTIMATION OF GASOLINE LEAD CONTRIBUTIONS TO ADULT BLOOD LEAD BURDENS BASED ON ILE STUDY RESULTS

As discussed in Chapter 11 (pp. 11-118 to 11-123) the results of the Isotopic Lead Experiment (ILE) carried out in Northern Italy provide one basis by which to estimate contributions of lead in gasoline to blood lead burdens of populations exposed in the ILE study area. Figures 1 to 5 of this appendix, reprinted from the ILE Status Report (1982) illustrate changes in isotopic lead (206/207) ratios for 35 adult subjects, for whom repeated measurements were obtained over time during the ILE study. The percent of total blood lead in those subjects contributed by Australian lead-labelled gasoline (petrol) used in automotive vehicles in the ILE study area was estimated by the approach reprinted below verbatim from Appendix 17 of the ILE Status Report (1982):

The main purpose of the ILE project was the determination of the contribution of petrol lead to total lead in blood. A rough value for the fraction of petrol lead in blood can be derived from the following equations:

$$R_1 X + f (1-X) = R' \quad (I)$$
$$R_2 X + f (1-X) = R'' \quad (II)$$

each of them referring to a given time at which equilibrium conditions hold.

R' and R" represent the blood lead isotopic ratios measured at each of the two times; if R_1 and R_2 represent the local petrol lead isotopic ratios measured at the same times, X is the fraction of local petrol lead in blood due to petrols affected by the change in the lead isotopic ratio, irrespective of its pathway to the blood i.e. by inhalation and ingestion (e.g. from petrol lead fallout). The term (1-X) represents the fraction of the sum of all other external sources of lead in the blood (any <<other>> petrol lead included), factor f being the unknown isotopic ratio of the mixture of these sources. It is assumed that X and f remained constant over the period of the experiment, which implies a reasonable constancy of both the lead contributing sources in the test areas and the living habits which, in practice, might not be entirely the case.

Data from individuals sampled at the initial and final equilibrium phases of the ILE study together with petrol lead isotopic ratios measured at the same times, would ideally provide a means to estimate X for Turin and countryside adults. However, for practical reasons, calculations were based on the initial and final data of the subjects whose first sampling was

done not later than 1975 and the final one during phase 2. Their complete follow-up data are shown in Table 27. For R_1 and R_2 the values measured in the phases 0 and 2 of ILE were used (R_1 = 1.186, R_2 = 1.060). Hence, as averages of the individual X and f results, we obtain:

Turin	$X_1 = 0.237 \pm 0.054$ $f_1 = 1.1560 \pm 0.0033$	i.e 24%
countryside <25 km	$X_2 = 0.125 \pm 0.071$ $f_2 = 1.1542 \pm 0.0036$	i.e. 12%
countryside >25 km	$X_3 = 0.110 \pm 0.058$ $f_3 = 1.1576 \pm 0.0019$	i.e 11%

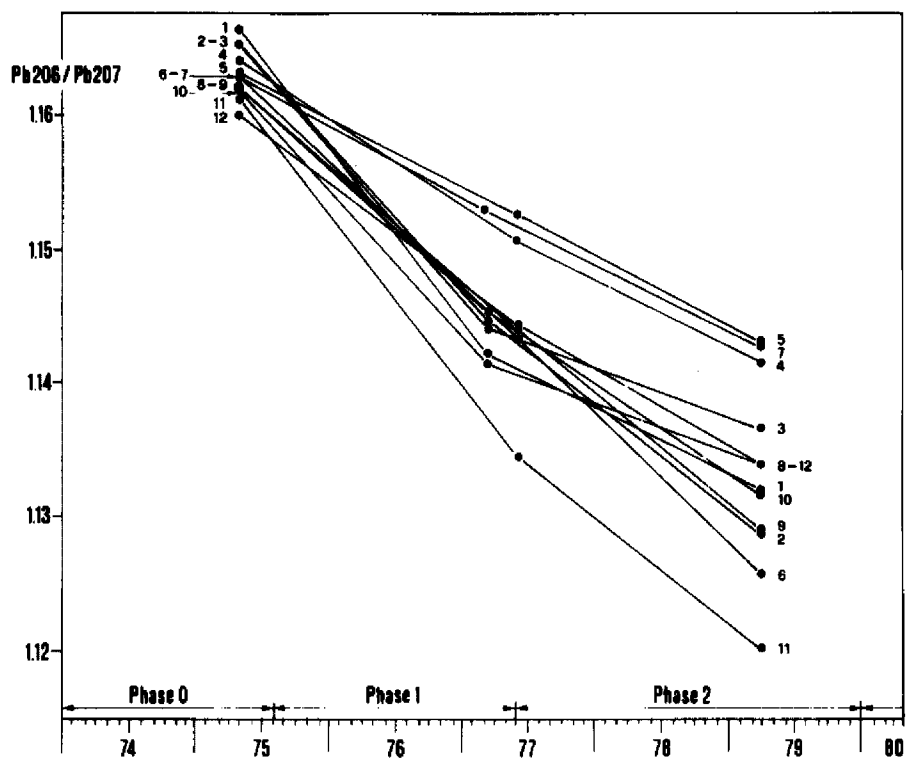

Fig. 1. Individual values of blood Pb-206/Pb-207 ratio for subjects follow-up in Turin (12 subjects)

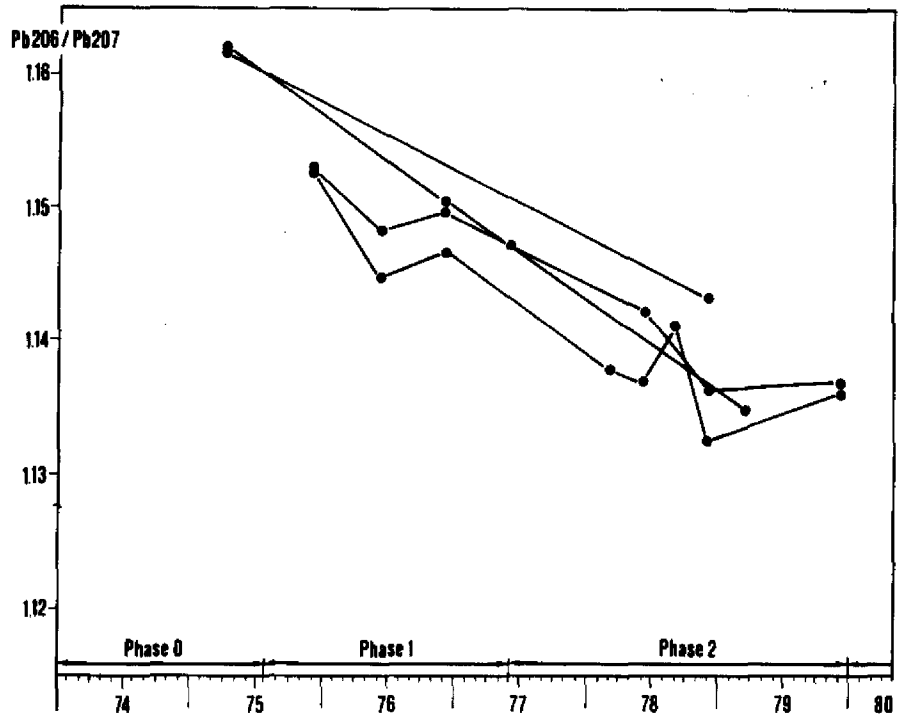

Fig. 2. Individual values in blood Pb-206/Pb-207 ratio for subjects follow-up in Castagneto (4 subjects)

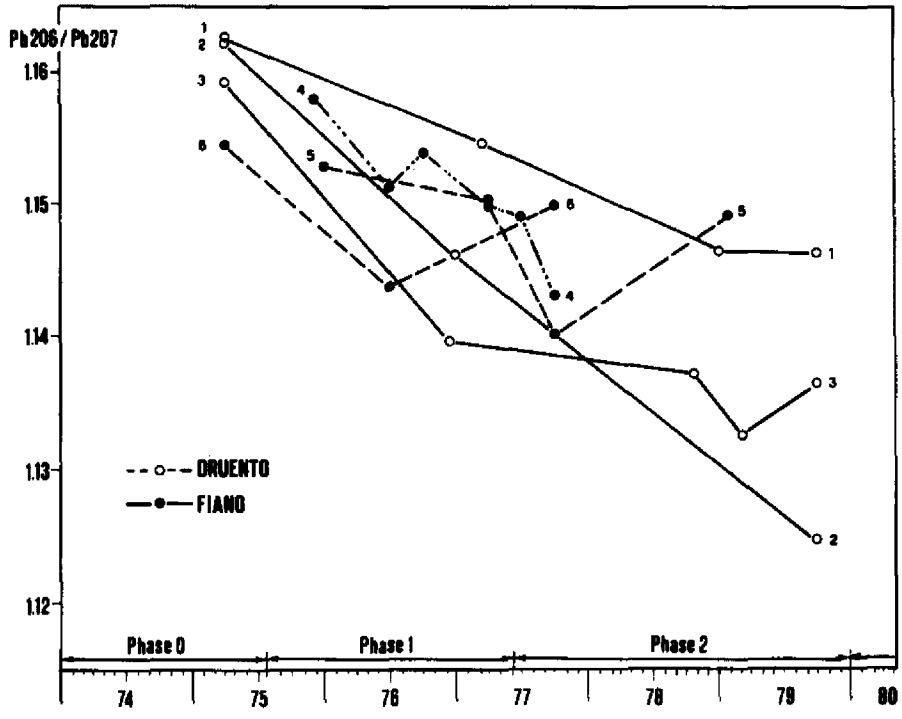

Fig. 3. Individual values of blood Pb-206/Pb-207 ratio for subjects follow-up in Druento and Fiano (6 subjects)

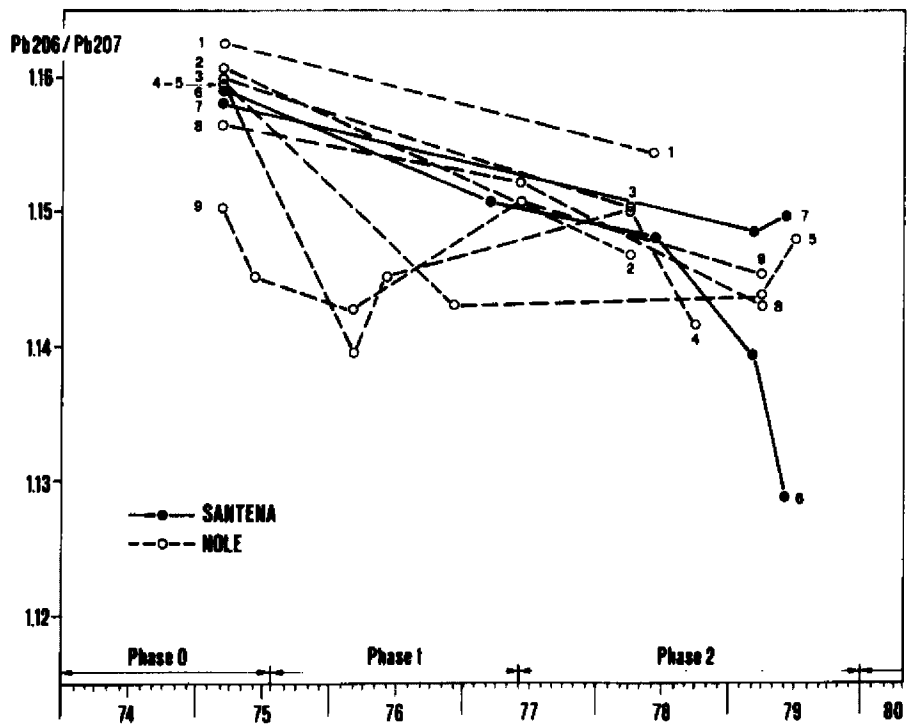

Fig. 4. Individual values of blood Pb-206/Pb-207 ratio for subjects follow-up in Nole and Santena (9 subjects)

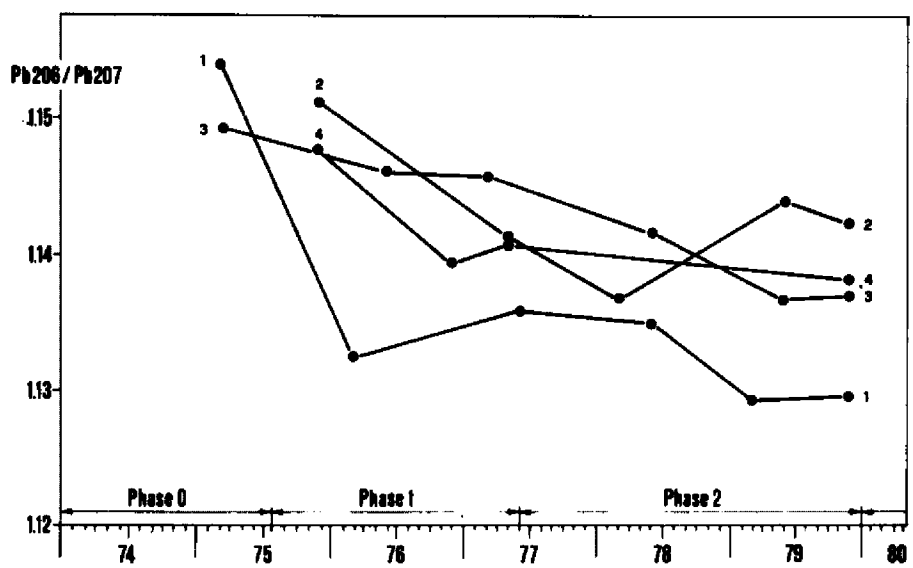

Fig. 5. Individual values of blood Pb-206/Pb-207 ratio for subjects follow-up in Viù (4 subjects)

APPENDIX 11-D

REPORT

OF THE

NHANES II TIME TREND ANALYSIS REVIEW GROUP

June 15, 1983

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Environmental Criteria and Assessment Office (MD-52)
Research Triangle Park, North Carolina 27711

The materials contained in this report were generated as the result of critical evaluations and deliberations by members (listed below) of the NHANES II Time Trend Analysis Review Group. All members of this Review Group unanimously concur with and endorse the findings and recommendations contained in the present report as representing the collective sense of the Review Group.

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Summary

The Review Group finds strong evidence that there was a substantial decline in the average level of blood lead in the U.S. population during the NHANES II survey period. After adjustment for relevant demographic covariables, the magnitude of the change can be estimated for the total U.S. population and for some major subgroups, provided careful attention is given to underlying model assumptions.

The Review Group also finds a strong correlation between gasoline-lead usage and blood-lead levels. In the absence of scientifically plausible alternative explanations, the hypothesis that gasoline lead is an important causal factor for blood-lead levels must receive serious consideration. Nevertheless, despite the strong association between the decline in gasoline-lead usage and the decline in blood-lead levels, the survey results and statistical analyses do not confirm the causal hypothesis. Rather, this finding is based on the qualitatively consistent results of extensive analyses done in different but complementary ways.

The gasoline lead coefficient in regressions of blood-lead levels on that variable, adjusted for observed covariates, has been used to quantify the causal effect of gasoline lead on blood-lead levels. The Review Group considers that such inferences require strong assumptions about the absence of effects from other unmeasured lead sources, the adequacy of national gasoline lead usage as a proxy for local exposure, and the adequacy of a sample design which does not measure changes in blood-lead levels for individuals in the sample. The validity of these assumptions could not be determined from the NHANES II data or from other data supplied to the Review Group. Furthermore, the Review Group cautions against extrapolation of the observed relationship beyond the limits of the four year period.

Introduction

This Review Group was appointed in February, 1983 by the Director of the Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency (EPA), to consider a series of questions about the interpretation of data from the second National Health and Nutrition Examination Survey (NHANES II) to evaluate relationships over time between blood-lead levels and gasoline lead usage. The questions addressed to the Review Group are listed in full in Appendix D1.

Documents describing NHANES II, analyses of the survey data, and analyses of the relationships between blood-lead values and gasoline lead usage were furnished for review. In two meetings, on March 10-11 and March 30-31, 1983, the Review Group discussed these materials with officials of the EPA, and with specialists from the several institutions that had conducted these studies. The documents provided for review are listed in Appendix D2. The individuals who attended the two meetings are listed in Appendix D3.

The panel members of the Review Group are statisticians with experience in applications of statistics in the physical, biomedical, and social sciences, but had no previous involvement in analyses of data about blood lead or gasoline lead. The affiliations of the panel members are listed in Appendix D3 for identification; views expressed by the panel in this report are their own and not those of the institutions.

Agencies involved in the conduct of the NHANES II were the National Center for Health Statistics (NCHS), the Centers for Disease Control (CDC) where the chemical analyses were done, and the Food and Drug Administration (FDA).

Contributors to the analysis of the association between blood lead and gasoline lead usage, in addition to NCHS and CDC, are E. I. DuPont de Nemours & Co. (DuPont), The Ethyl Corporation (Ethyl), and the EPA Office of Policy Analysis working in collaboration with ICF Incorporated (ICF) and Energy and Resource Consultants, Inc. (ERC).

This report contains two major sections. The first, on time trends in blood-lead levels, addresses a set of questions about the use of NHANES II data to estimate changes over time. The second addresses statistical aspects of evaluating the relationship of changes in blood-lead levels to gasoline lead usage.

Time Trends In Blood-lead Values

At its first meeting on March 10-11, 1983, the Review Group considered only the first of the set of questions presented to it (see Appendix D1), namely questions about the extent to which the NHANES II data could be used to "determine time trends for changes in nationally representative blood-lead values for the years of the study (1976-1980)."

The phrases "define time trends" and "determine time trends ... (1976-1980)" are interpreted throughout this report to mean "estimate changes in blood-lead values during the survey period." In particular, such changes are not to be interpreted as trends that might be extrapolated.

The Group recognized that the survey was designed as a cross-sectional survey, and specifically inquired into three general kinds of possible sources of time-related bias:

- the measurement quality control,
- the nonresponse experience, and
- the survey design.

As would be expected, only incomplete evidence could be made available in each of these areas. The following assessment of this evidence indicates where it depends on the expert opinion of others.

Measurement Quality Control

In order to analyze the time trends in NHANES II data, one must assume that the procedures for collecting, handling, and analyzing blood specimens did not change during the survey years. The Review Group is aware that contamination can produce spuriously high values in determination of trace elements, and sought evidence that quality control procedures were equally stringent at all times.

Although no quality control specimens were prepared at the medical examination sites, the Review Group has been assured that training, periodic retraining, materials, equipment, and procedures were designed to prevent contamination, and not changed. There was some turnover of personnel.

The CDC laboratory established and documented the results of extensive quality control sampling (App. D2, item 14). The data on lead levels in the "blind" samples, from two pools of bovine blood, exhibit essentially constant means and standard deviations. The coefficient of variation for measurement error was found to be about 17 percent for blood-lead levels near 13 µg/dL; it was smaller, about 13 percent, for higher blood-lead levels near 25 µg/dl. Additional evidence of the constancy of quality control is that data from other analyses of the blood specimens (zinc, for example) exhibit little or no change over time.

The Review Group finds no evidence that field and laboratory quality control changes could account for the observed change in blood-lead levels.

Nonresponse

Nonresponse is an important potential source of bias in sample surveys. It is of particular concern in the blood-lead analysis of the NHANES II since the nonresponse rate is high--39.3 percent of sampled persons had missing lead values due to nonresponse at various stages of participation in the survey (App. D2, item 14, p.9). The NCHS attempted to adjust for nonresponse by weighting responding individuals by estimates of the probability of response, calculated within subclasses of the population formed by joint levels of age, income, SMSA/non-SMSA, and region.

This is a standard adjustment method for unit nonresponse in surveys. The method adjusts for differential nonresponse across the subclasses used to calculate the weight, but does not account for residual association between nonresponse and time and blood-lead level, which are the variables of primary interest in the analysis under consideration. Thus there is the possibility that nonresponse bias is a contributory factor to the trend in blood-lead levels across time.

In order for nonresponse to have this effect it is necessary that, after adjusting for the socioeconomic variables used to define the weights, nonresponse be related to blood-lead level, and further that this relationship change over time, so that a differential bias in the mean blood-levels of respondents exists across time. Clearly this question cannot be addressed directly, since the blood-lead levels of nonrespondents are not measured. However, the Review Group considered such an interaction to be highly unlikely, for the following reasons:

- Nonresponse rates did not vary in a consistent way across time. Examination of changes in response rates does not indicate any relationship of importance (App. D2, item 18).

- There does not appear to be evidence that the conditions of the survey changed significantly across time, so that any bias introduced by an association between nonresponse and blood-lead level is unlikely to change across time.

Accordingly, the Review Group rejected nonresponse as a likely explanation for the trend observed in the data.

Survey Design

The NHANES II was designed to provide U.S. national prevalence rates for a wide range of characteristics and health conditions. Due to financial and logistical constraints, the survey design required a four-year data collection period. Consequently, the sample quantities, such as the blood-lead levels, necessarily will provide period prevalence estimators, rather than point prevalence estimators of the underlying population parameters. In general practice, a fundamental assumption underlying the use of period data to generate prevalence estimators is that the condition under investigation remains relatively constant throughout the survey period.

Even though the NHANES II was not designed to detect and estimate changes in prevalence throughout the survey period, one must consider the possibility that the level of a particular target characteristic, such as blood lead, actually may be changing over time. Consequently, one cannot ignore evidence suggesting that the level of lead in blood in the U.S. population was decreasing during the data collection period simply because the survey design was cross-sectional, rather than longitudinal. Rather, the difficult question is to what extent, if any, can these NHANES II data be used to determine time trends.

Although a cross-sectional design such as the one utilized in the NHANES II certainly is not optimal for investigating time trends, one can consider making adjustments within the sample for the effects of relevant covariables such as age, sex, race, residence, and income, if the distributions of these covariables are not highly confounded with time. An additional requirement for making adjustments is that there be reasonably large numbers of sample persons for different covariable levels at various times. These internal adjustments permit one to examine whether the decline in blood-lead levels can be accounted for by differing proportions of individuals from subgroups determined by relevant covariables. The extent of this type of selection bias over time relative to primary demographic characteristics can be summarized (App. D2, item 20, Tables M7, M8 for whites, and M13, M14 for blacks).

The Review Group considered carefully the potential bias due to changing composition of the sample over time, especially since this had been emphasized by Ethyl (App. D2, items 25, 26). The most striking problem occurs with urban vs. rural groups. The fractions of blood samples obtained from white urban residents are shown as follows:

	% urban bloods	Sample size
Jan - Jun 1976	64.2	795
Jul - Dec 1976	36.9	1255
Jan - Jun 1977	44.6	935
Jul - Dec 1977	57.3	1010
Jan - Jun 1978	46.3	1056
Jul - Dec 1978	40.6	981
Jan - Jun 1979	31.6	1228
Jul - Dec 1979	20.7	842
Jan 1980	0.0	267

Thus, there has been a striking decrease in the number of bloods taken from white urbanites across the four years. If one assumes that exposure to lead from gasoline is more prevalent in urban areas, then (without adjustment) the observed mean blood levels across the four years would be biased because of the NHANES II schedule.

Further examination of the CDC tabulation (App. D2, item 20) indicates sparse information on blacks. The numbers are so small that time trend inferences for blacks can be estimated with confidence only for overall mean blood-lead level results without regard to sex, place of residence, and age.

The Review Group finds that despite obvious trends over time for such characteristics as degree of urbanization and the proportion of children aged 0.5 to 5 years, the sample size is distributed across the grid of covariable levels sufficiently to permit reasonable adjustments. In support of this finding, the Review Group notes that similar trends appeared whenever demographic subgroups were examined separately. These subgroups included white males, white females, white children, white teenagers, white adults, and blacks, as well as breakdowns by income and urban-rural status.

Sample Weights

Another possibility is that the sample mean blood-lead level changes resulted from trends in more subtle statistical characteristics of the sample over time, such as characteristics related to the way sample weights are used to calculate averages. But this explanation appears to be inconsistent with the fact that analyses of the unweighted NHANES II data lead to essentially the same results as the weighted data and analysis.

In response to questions raised by both industry representatives and other observers, the Review Group explored the effects of the complex weighting scheme inherent in all the CDC and EPA/ICF analyses. Each sample observation has both a basic weight (related to the probability of selection), a final weight (reflecting additional adjustments to the basic weight accounting for nonresponse patterns of selected demographic subgroups), and a final examined lead subsample weight (corresponding to the entire set of adjustments due to the probability of selection, nonresponse, and post-stratification, and the subsampling of individuals selected for the measurement of blood lead). All the weighted analyses in the CDC and EPA/ICF reports were conducted relative to the final examined lead subsample weight.

One potential problem associated with this final lead subsample weight is the possibility that differential nonresponse patterns for various demographic subgroups may lead to marked differences between the basic weight (without nonresponse adjustments) and this final weight. For that reason, the Review Group requested a data display of the total nonresponse rate and the average blood-lead levels by the 64 separate stands using three different weighting schemes in computing the averages:

i) unweighted;
ii) basic weights;
iii) final lead subsampling weights.

As shown in Table 1, item 18 of App. D2, the average blood-lead levels are quite consistent under each weighting scheme for each of the 64 stands. Furthermore, there is no apparent trend in the nonresponse rate across time. Consequently, one would expect that an analysis of these data under the basic weights also would parallel the results obtained in the CDC and the ICF reports.

These findings, in conjunction with the similarities between the weighted and unweighted analyses, lend additional support to the overall consensus among panel members that these data analyses are not dependent on the particular choice of weights, including the intermediate basic weights.

Estimated Time Trends

There seems to be no doubt that, qualitatively, a downward trend of blood-lead levels has been observed during the NHANES II survey.

The data appear to support reasonably precise estimates of the magnitude of the change for a few major subgroups of the population. In particular, the change in mean blood-lead levels during the survey period can be estimated for the population as a whole and for population sectors grouped by age, sex, race, urban/rural, and income, if each of these demographic categories is considered separately.

For estimating changes in mean blood-lead levels for combinations of demographic factors, sufficient data appeared to be available for white-by-sex and white-by-age breakdowns. These estimated changes, and others that might be considered, can be made on the basis of a linear model that provides adjustments for demographic and socioeconomic covariables that are known or believed to be associated with blood-lead levels.

For finer subdivisions, estimates of change are subject to large sampling error and are sensitive to correct specification of the regression model. Hence, caution must be exercised in their interpretation. It is not possible to show time changes in mean blood levels for specific cities, towns, or locales using the NHANES II data, since no city or locale was sampled more than once. No data which would allow estimates of time trends in mean blood-lead levels for different occupational categories were shown to the Review Group. The only socioeconomic variable considered was income.

Estimates of change, e.g., those reported by CDC (App. D2, item 14, Table 6, page 44), should be accompanied by standard errors. There should be discussions of the use of regression diagnostics to evaluate the adequacy of the model, and the possibility that a few observations exert an excessive influence on the result. The calculation of standard errors should use procedures that take into account the stratification and clustering properties of the survy design. In response to the Review Group's questions, CDC provided a document presenting standard errors and the methodology used to estimate them (App. D2, item 38). The size of these standard errors suggests that there are only weak indications of differences between subgroups with respect to the percent drop in the average blood-lead level.

Summary

Although the survey was not specifically designed to measure trends, data from the NHANES II can be used to estimate changes in blood-lead levels during the four-year period, 1976-1980, of the survey. Changes can be estimated for the U.S. population and for major population subgroups, as specified in the previous subsection. Because of sampling error, laboratory measurement error, a high nonresponse rate, and the need to adjust for time-related imbalance in the survey design, such estimated changes should be interpreted with caution.

Correlation Between Blood-Lead and Gasoline-Lead Changes

At its second meeting on March 30-31, 1983, the Review Group considered three sets of studies that examine the association between changes in blood-lead levels estimated from the NHANES II data and changes in the use of leaded gasoline:

- the Ethyl Corp. analysis (App. D2, items 25, 26)
- the ICF/EPA analysis (App. D2, items 11, 22, 23, 24), and
- the CDC/NCHS analysis (App. D2, item 14 and appendices).

The following discussions summarize the Review Group's assessment of the strengths and weaknesses of the analyses.

Preliminary Remarks

The analyses propose and evaluate models for the relationship between blood-lead levels and gasoline-lead usage. All of these analyses rely on multiple linear regression methods, whose limitations with respect to establishing causal relations are well known (See, e.g., reference 1). The statistician-reviewer may adopt one or the other of two approaches in considering the strengths and weaknesses of the several analyses:

(1) Assume (on external authority) the existence of a causal relationship between gasoline lead usage and blood lead levels. Consider the variables and models used to analyze the strength of the association and to estimate the effect of gasoline-lead changes on blood-lead changes. In this approach, the possible effects of other changes over time that affect blood-lead levels are treated as second-order effects. CDC urges this approach.

(2) Adopt a neutral position as to the causal relationships, and examine the associations among the variables studied. In this approach, "time" serves as a proxy for the combined effect of whatever changes affected blood-lead levels and it is left to the interpreter of the analyses to assign relative importance among suggested explanations for changes over time. DuPont and Ethyl suggest this approach.

The ICF and CDC analyses both found a clear relationship between gasoline lead and blood lead. The Ethyl analysis found no evidence of association between these variables. The purpose of this commentary is to discuss the important differences between the analyses and to assess their utility in establishing or contradicting the hypothesized relationship between the decline in blood-lead levels and the decline in gasoline lead emissions over the period of the NHANES II Survey.

Table I (next page) classifies the three analyses by six factors which capture the main differences between them, namely: 1) the choice of measure of gasoline lead, 2) the scale of blood lead variable, raw or logarithm, 3) the unit of analysis, 4) control variables in the regression, and in particular

the inclusion or omission of a time variable, 5) the weighting used in the regressions, and 6) the method used to calculate standard errors. The panel concludes that of these factors only (1) and (4) had a substantial impact on the final results.

Table 1

	CDC	ICF	Ethyl
1) measure of gasoline lead	quarterly	monthly sales x lead conc.	pop. density local lead usage
2) scale of dependent variable	log	raw	raw
3) unit of analysis	individual	individual	individual stage 1 locality stage 2
4) control variables include time	no	time, season, lagged gas	time
5) weighting by selection probs.	both	yes	no
6) design based standard errors	yes	yes	no

The first three factors are discussed under the heading "Variables Used in the Analyses". Factors (4), (5), and (6) are discussed under "Statistical Techniques Used in the Analyses". Factor (4) is considered further in the assessment of "Models Used in the Analyses".

Variables Used in the Analyses

Demographic and socioeconomic covariables were used as defined for the NHANES II Survey. Differences between the analyses occurred in the choice of specific representations for blood-lead levels and gasoline lead usage.

Blood Lead. All the studies used blood-lead values for individuals from the NHANES II Public Use Data Tape, with associated demographic, economic, time, and sampling-weights data.

Ethyl calculated adjusted blood-lead values for its principal analysis by fitting a linear model to adjust for age, sex, race, and income to obtain the residuals from this analysis. Ethyl did not adjust the individual data for the effect of the degree of urbanization, a factor recognized to be related to blood-lead levels. Averages of the adjusted values for 55 of the 64 examination sites were used in the principal (second-stage) analysis.

ICF used the NHANES II blood leads without adjustment or transformation. Adjustment for socio-demographic variables was achieved by including these variables as covariates in regression models for individual blood leads.

CDC adopted a similar approach, but used the natural logarithms of the NHANES II blood leads, on the basis of an analysis showing that the distribution of the values themselves was skewed and that the transformation successfully corrected for the skewness.

The scale of the dependent variable (raw or logarithm) does not appear to have a great influence on the final results. With the exception of race, the blood-lead/gasoline-lead slope in the CDC and ICF analyses appeared stable across demographic factors, whether the raw or log scale was used for the dependent variable. The logarithm scale has the advantage of being more likely to yield normal residuals.

The unit of analysis (factor 3) received a considerable amount of discussion by reviewers. In particular, the Ethyl two-stage analysis was subjected to some criticism. At the first stage, the blood lead variable was adjusted for differences in the distributions of demographic variables by an individual level regression on NHANES II data. At the second stage, the adjusted locality mean blood-lead values were regressed on proxies for gasoline lead which had not themselves been adjusted for the demographic variables. This two-step regression procedure leads to bias (see reference 2), but the bias does not appear important, as Ethyl later corrected the analysis with no substantial change in the results.

Gasoline Lead Usage/Exposure. There were several different approaches to defining variables that could be interpreted as indexes of the amount of lead present in the environment at the time when blood samples were taken, as well as during the antecedent months. Clearly, no index number or set of index numbers can serve as an ideal surrogate for a measurement of the exposure experiences of sampled persons. The Review Group recognizes the complexity of the mixture of lead sources and uptake pathways.

The large differences between the results of the ICF/CDC analyses and the Ethyl analysis are caused by different measures of gasoline lead exposure. ICF and CDC used national period measures-quarterly EPA lead additive data for CDC and adjusted monthly gasoline sales data for ICF, whereas Ethyl used two proxy measures for lead exposure at each locality--population density and lead use per unit area.

A fundamental assumption underlying the creation of a local estimate of gasoline lead exposure is the notion that the volume of leaded gasoline consumed locally, with the resulting "fallout", is the primary source of lead in human blood. Although this determination requires substantive expertise beyond that on our Review Group, the choice of a local vs. a global measure of exposure is a pivotal one in all these analyses. If, in fact, lead enters the human blood system via imported fallout through the food chain (and other sources), as well as the inhalation of local "fallout", then ideally one would require a summary measure of exposure which captures both of these sources.

CDC used data from the quarterly EPA Lead Additive Reports (App. D2, item 14, pages 37-40 and Appendix H). These are national values of the total amount (by weight) of lead used in gasoline production. The series exhibits seasonal fluctuations in gasoline production in addition to a general downward trend.

ICF developed a monthly series of national values of the average amount (by weight) per day of lead used in gasoline, as follows: Monthly average gasoline use (liquid volume per day) was obtained from the DOE Monthly Energy Review. Quarterly values of the concentration of lead in gasoline (grams per gallon, based on refiner reports) were obtained from EPA (App. D2, item 11). The product of these produced a monthly series. This series, if aggregated to a quarterly series, would be closely related to the series used by CDC.

The measures of lead use used by CDC and ICF capture the downward trend in gasoline lead over time, but they suffer from specification error in that they are national rather than localized measures of gasoline lead exposure. The defect has two consequences:

(a.) The gasoline lead use variable does not capture variation in gasoline lead exposure between localities.

(b.) The lead use variable can be only partially adjusted for correlations with the demographic covariates.

The CDC analysis partially corrects for (a) by aggregating the gasoline lead exposure over all sampled localites in a six month period of sampling. The second problem remains, however. The panel does not believe that these deficiencies invalidate the qualitative findings of a relationship between lead usage and blood lead. However, the impact on the coefficient of lead usage in the CDC analysis is not clear.

Ethyl adopted a different approach, seeking to represent gasoline-lead usage at the survey locations and also to consider separately the effects of lead in air and lead fallout. The variables used to represent the two kinds of lead exposure were, respectively, population density and gasoline lead usage per square mile for the sampled localities.

The Review Group applauded the intention of the Ethyl effort, but the variables selected appear to be inappropriate. In the Ethyl discussion (App. D2, item 26, Appendix page A-3) it is pointed out that population density is strongly related to degree of urbanization, a factor for which adjustment is made in the CDC and ICF analyses, but not in the Ethyl analysis. Furthermore, Ethyl calculated population density by interpolation between censuses and it is doubtful that it would reflect changes (if any) in the concentration of lead in air within the four-year survey period.

Ethyl represented lead usage per unit area by annual values by state. Department of Transportation reports of annual gasoline sales (by state) and annual Ethyl estimates of the amount of lead in gasoline being sold (by state) produced state estimates of annual totals of lead used. These were then divided by the area of the state. Examination of the resulting values (App. D2, item 26, Table 6, page 23) reveals anomalies. For example, the 1979 lead usage value for Washington, DC, is 5 times larger than that for any other

location. The second-largest value is the one for New Jersey in 1977, used for locations adjacent to New York City; it is more than 4 times the 1977 value used for both New York City and its Westchester County suburbs. As another example, the computed exposure for Houston, TX (ID no. 28) is 101, compared to 7174 for Washington, DC (ID no. 33). The naive implication of these two data points is that persons living in Washington, DC received a 71-fold (7174/101) increase in dosage of air-lead (or food chain lead) compared to persons living in Houston, TX. Whether we view this dosage as exposure through air or food, this extreme differential is highly unlikely. This variable appears to represent chiefly the statewide average population density. The Review Group cannot accept it as an indicator of gasoline lead usage at the sample locations.

Statistical Techniques Used in the Analyses

All final models reported by EPA/ICF and CDC were fitted to the NHANES II data using the SURREGR procedure available in SAS. This computing software permits sample weights and cluster design effects to be incorporated into the variance-covariance estimators of the model parameters. Although unweighted and weighted ordinary least squares model fitting provided the same conclusions, SURREGR provides better estimates of standard errors for these complex survey data. This estimation and hypothesis testing strategy is the most conservative approach, since it will produce larger standard errors for the parameter estimates due to the clustering in the data. Extensive empirical investigations of the role of weights and design effects in the NHANES I survey demonstrated that test statistics are decreased when including weights, and decreased even further when adjusting for design effects (see reference 3).

The two-stage procedure adopted by Ethyl was described in the preceding subsection.

Models Used in the Analyses

There is no unique correct approach to analyzing the relationships within the NHANES II data or between the NHANES II and other data sets. For this reason, it has been useful to compare and contrast a variety of approaches and models.

All of the models have the general character that a measure of blood lead is expressed as a linear combination of a measure (or measure) of exposure to gasoline lead with various demographic and socioeconomic covariables and (sometimes) time.

The primary difficulty with the Ethyl analyses (App. D2, item 26) lies in the choice of constructed gasoline-lead variables. Neither the population density variable (C19) nor the lead usage variable (C16) is an acceptable measure of gasoline lead exposure.

The Ethyl report concludes with the observation

> In summary, our analysis of the NHANES II data has shown that time (T) is the major contributor to differences in blood lead between

> 1976 and 1980 ... The major contribution of time to the decrease in blood lead indicates that other factors that vary with time are the major causes of the 1976 to 1980 decrease in blood lead and not gasoline lead usage.

Ironically, national gasoline lead usage (as defined in the CDC or ICF analysis) is such a variable that varies with time and is known to be causative of some portion of the lead in blood. The constructed variable (C16) does not display a similar relationship with time.

The CDC and ICF/EPA analyses are similar in their general approach. In each case, a variety of models was considered (adding and deleting various subsets of the covariables and interaction terms). These variations had only minor impact on the value of the coefficient for the lead usage variable.

Although both the CDC and EPA/ICF analyses used national data on leaded gasoline sales, the EPA/ICF models utilized a gasoline lead use variable which was estimated at each month of the survey (App. D2, item 11, Table 1, pp. 13-14). Consequently, since the data collection period for most of the 64 stands in the NHANES II survey spanned across two months, the gasoline lead use variable could, and in some cases did, assume two different values for the same site, according to the month of examination. Investigations of the relationships between time and blood-lead levels involved comparisons within sites (due to spanning two months), as well as among sites. Thus, even though there is a high degree of correlation between time and gasoline lead usage, these two variables are not completely confounded with the 64 different sites.

It is, nevertheless, a significant question whether the time variable is included in the model as a covariate. The ICF analysis included a linear time covariable and seasonal effects in the model, "to give the models the ability to attribute temporal variations in blood lead to effects other than gasoline lead" (App. D2, item 11, p. 8). Variables for time and gasoline lead were not included simultaneously in the CDC analysis.

The intent of the ICF procedure is reasonable, but the confounding between time and gasoline lead in the data make the simultaneous inclusion of these variables in the model questionable. The data do not allow the relationship between gasoline lead and blood lead to be estimated at any particular time point. Thus the attempt to adjust for time is highly dependent on the specification of the time effects in the model. Despite these problems, two aspects of the ICF analysis yielded some circumstantial evidence that gasoline lead is an important agent of the trend in blood lead. The gasoline lead variable accounted for seasonal variation in blood lead, and the lagged gasoline lead variables provided a plausible lag structure: the one-month lagged variable had the strongest association with blood lead.

Gasoline Lead as a Causal Agent for the Decline in Blood-Lead Levels

The CDC and ICF analyses provide strong evidence that gasoline lead is a major contributor to the decline in blood lead over the period of the NHANES study. DuPont stressed the limitations of statistical theory and methods as tools for assessing causal relationships.

Analysis of the NHANES II data cannot prove whether changes in the use of leaded gasoline caused a change in average blood-lead levels. Variables X and Y can be correlated because changes in X cause changes in Y, or vice versa, or because some third factor, Z, affects both X and Y. There are many other possibilities as well, but these are enough for this discussion. If X stands for some measure of average blood lead concentration and Y stands for the amount of lead in gasoline, we can dismiss the first possibility as absurd. But the relative plausibility of the other two is a matter for expert scientific judgement. To date, no hypothesis of the third form which could explain the NHANES II data has been presented to the panel. One hypothesis of this form has been discussed. This hypothesis has Z representing regulatory changes and publicity aimed at reducing lead exposure generally. This could result in reductions in gas lead, lead in food, lead in paint, etc., and it could be that the gas lead change had little effect on blood-lead levels -- the blood-lead changes might have been caused by the other factors (food, paint, etc.). Although this hypothesis cannot be disregarded entirely, it does not seem to explain the blood-lead drop adequately. We have seen little evidence that food lead has dropped by a factor large enough to explain a sizable part of the drop in blood lead. In fact, the FDA diet lead values shown in the ICF Report (App. D2, item 11, Table 2) were increasing during the study period. That changes in exposure to leaded paint caused the decrease in blood-lead observed over all age and sex groups seems highly unlikely. The existence of influences (other than gasoline lead usage) that are not included in the models must be recognized as a limiting factor in the evaluation of all of the analyses.

Use of NHANES II Data for Forecasting Results of Alternative Regulatory Policies

Regression models have been used in all three analyses to see if the NHANES II time trend in average blood-lead levels can be explained in terms of changes in demographic variables or in terms of changes in gas and lead usage. Extension of the use of these and other statistical techniques "to estimate the distribution of blood-lead levels of whites, blacks, and black children and to forecast the results of alternative regulations," as in Section III of the ICF Report of December, 1982 (App. D2, item 11), raises questions and involves assumptions that go much further than those the Review Group was able to consider. In general, the Review Group would warn that the weaknesses that have been discussed in the context of analyzing relationships within the four-year survey period become enormously greater in any attempt to extrapolate beyond that period. For example, the cautions mentioned in the ERC review (App. D2, item 22, p. 6) of the ICF analysis probably do not go far enough.

Summary

In general, there is a significant correlation between gasoline-lead levels and blood-lead levels in persons examined in the NHANES II Survey. Major obstacles interfere with the use of the available data to describe the relationship. They are: the need to perform model-based adjustments to compensate for imbalance in the design of the NHANES II, the possibility of specification error in the regression models, and the lack of a satisfactory measure of individual or local exposure to gasoline lead, in addition to sampling error, laboratory measurement error, and the high nonresponse rate.

The Review Group finds that the Ethyl analyses contribute little to understanding the association between blood lead and gasoline lead because the variables adopted to represent lead exposure are deemed inappropriate.

The CDC and ICF/EPA analyses relating the NHANES II blood-lead data to a national measure of the amount of lead used in gasoline indicate that the drop in average blood-lead levels can be explained, in large part, by the concurrent drop in gasoline lead. This by no means confirms the hypothesis that the blood lead decrease was caused by the decrease in gasoline lead but, in the absence of scientifically plausible alternative explanations, that hypothesis must receive serious consideration.

References

Literature cited in this report, in addition to the documents furnished by the EPA which are listed in Appendix D2.

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(3) Landis, J. R., Lepkowski, J. M., Eklund, S. A. and Stehouwer, S. A. (1982). A General Methodolody for the Analysis of Data from the NHANES I Survey. Vital and Health Statistics, NCHS Series 2- No. 92. DHHS Publ No. (PHS) 82-1366. Washington. U.S. Government Printing Office.

Appendix D1

Questions for the Review Group

The following questions were stated in letters to members of the Review Group from Dr. Lester D. Grant, Director of the EPA Environmental Criteria and Assessment Office, February 17, 1983.

1. To what extent is it valid to use the NHANES II data to determine time trends for changes in nationally representative blood-lead values for the years of the study (1976-1980)? More specifically, to what extent can the NHANES II data appropriately be used to define time trends for blood-lead levels (aggregated on an annual, semiannual, or any other time-related basis) for the total NHANES II sample (all ages, sexes, races, etc.) or for subsamples defined by the following demographic variables: (1) age (e.g., children <6 years old, children 6-12 years old, adults by 10- or 20- year age groups); (2) sex; (3) race; (4) geographic location (e.g., urban vs. rural residence; Northeast vs. Southeast, Midwest, or other large regional areas of the U.S.; residence in specific cities, towns, or rural locales); (5) socioeconomic status; (6) occupation of respondants or their parents/head of household at main residence; or (7) any combination of such demographic variables (e.g., black children <6 years or white children <6 years old living in urban or rural areas, etc.).

2. If it is indeed possible to derive such time trends from the NHANES II data, to what extent can the changes in NHANES II blood-lead levels over time be correlated credibly with changes in the usage of leaded gasoline over the same time period (i.e., the years 1976-1980)? Several analyses of this type have already been conducted and submitted to us, and we would appreciate your evaluation of those analyses.

3. Are there any other appropriate credible statistical approaches or analyses, besides those alluded to as already having been done, that might be carried out with the NHANES II data to evaluate relationships over time between blood-lead levels and gasoline lead usage?

Appendix D2

Documents Considered by
NHANES II TIME TREND ANALYSIS REVIEW GROUP

1. Plan and Operation of the Second National Health and Nutrition Examination Survey. (1976-1980) National Center for Health Statistics, Series 1, No. 15. July, 1981.

2. Public Use Data Tape Documentation. Hematology and Biochemistry, catalog number 5411. NHANES II Survey, 1976-1980, NCHS. July, 1982.

3. NHANES II Weight Deck (one record for each SP). Deck #502. Attachment I, NCHS.

4. NHANES II Sampling Areas. Document furnished by NCHS during site visit, March 10, 1983.

5. Steps in Selection of PSU's for the NHANES II Survey. Document furnished by NCHS during site visit, March 10, 1983.

6. Location of Primary Sampling Units (PSU) chronologically by pair of caravans: NHANES II Survey, 1976-80. Document furnished by NCHS during site visit, March 10, 1983.

7. Annest, J. L. et al. (1982) Blood lead levels for person 6 months - 74 years of age: United States, 1976-1980. NCHS ADVANCEDATA, No. 79, May 12, 1982.

8. Mahaffey, K. R. et al. (1982) National estimates of blood lead levels: United States, 1976-1980. Association with selected demographic and socioeconomic factors. New England Journal of Medicine 307: 573-579.

9. Average Blood Lead Levels for White Persons, 6 months - 74 years stratified chronologically by PSU's: NHANES II, 1976-80 by caravan. "Graph" furnished by NCHS, March 17, 1983.

10. Schwartz, J. The use of NHANES II to investigate the relationship between gasoline lead and blood lead. Memo to David Weil (ECAO) (March 3, 1983).

11. ICF Report: The Relationship between Gasoline Lead Usage and Blood Lead Levels in Americans: A Statistical Analysis of the NHANES II Data. December 1982.

12. Annest, J. L. et al. (1983) The NHANES II study. Analytic error and its effect on national estimates of blood lead levels.

13. Pirkle, J. L. Comments on the Ethyl Corp. analysis of the NHANES II data submitted to EPA October 8, 1982 (Feb. 26, 1983).

14. Pirkle, J. L. Chronological trend in blood lead levels of the second NHANES, Feb. 1976-Feb. 1980 (Feb. 26, 1983).

15. Lynam, D. R. Letter to David Weil dated October 15, 1982 containing additional comments on NHANES II data.

16. E. I. DuPont de Nemours & Co., Inc. Supplementary statement presented to EPA in the matter of regulation of fuel and fuel additives - lead phasedown regulations proposed rulemaking (Oct. 8, 1982).

17. Pirkle, J. L. An expanded regression model of the NHANES II blood lead data including more than 100 variables to explain the downward trend from Feb., 1976-Feb., 1980 (Dec. 23, 1982).

18. Annest, J. L. et al. Table 1. Average blood lead levels and total nonresponse rates for persons ages 6 months - 74 years stratified chronologically by primary sampling unit (PSU): NHANES II, 1976-1980 (Corrected version; April 8, 1983).

19. Pirkle, J. L. (1983). Duplicate measurements differing by more than 7 mg/dl in the lead measurements done in NHANES II Survey. Document furnished by CDC at Panels request, March 18, 1983.

20. Pirkle, J. L. Appendix M: Tabulation by demographic variables (March 18, 1983).

21. Pirkle, J. L. Appendix N: Regression analysis of urban and rural population subgroups (March 18, 1983).

22. Miller, C. and Violette, D. Comments on studies using the NHANES II data to relate human blood lead levels to lead use as a gasoline additive (March, 1983).

23. Miller, C. and Violette, D. (March 4, 1983). The Usefulness of the NHANES II Data for Discerning the Relationship between Gasoline Lead Levels and Blood Lead Levels in Americans and a Review of ICF's Analysis using the NHANES II Data. Energy and Resource Consultants, Inc.; Boulder, Colorado.

24. Schwartz, J. Analysis of NHANES II data to determine the relationship between gasoline lead and blood lead. Memo to David Weil (ECAO). (March 18, 1983).

25. Excerpt - (Section I. C. - "Discussion of NHANES II Blood Lead Data") from the Ethyl submission to the EPA's docket on the Lead Phasedown dated May 14, 1982.

26. Excerpt - (Section III. A. - entitled "Correlation of Blood Lead to Gasoline Lead" and Appendix "Discrete Linear Regression Study") from the Ethyl submission to EPA's docket on the Lead Phasedown. (October 8, 1982)

27. Ethyl Analyses of the NHANES II Data. This item was distributed at the Criteria Document meeting held on January 18-20, 1983.

28. Comments by Dr. Norman R. Draper on Ethyl Corporation's comments and ICF, Inc.'s comments.

29. Comments by Dr. Ralph A. Bradley entitled "A Discussion of Issues and Conclusions on Gasoline Lead Use and Human Blood Lead Levels".

30. Comments by Dr. Ralph A. Bradley in a letter to B. F. Fort. (Ethyl Corp.)

31. Ethyl Corp. NHANES II - blood lead data correlation with air lead concentration data.

32. Ethyl Corp. Summary of analyses of the NHANES II blood lead data (January, 1983).

33. E. I. DuPont de Nemours & Co. Comments submitted March 21, 1983.

34. E. I. DuPont de Nemours & Co. Comments by R. Snee and C. Pfieffer on paper by Annest et al. on analytic error (see item #5).

35. Pirkle, J. L. The relationship between EPA air lead levels and population density. (March, 1983).

36. Pirkle, J. Consecutive numbering of points on plots of 6-month average NHANES II blood lead levels versus 6-month total lead used in gasoline (April 11, 1983).

37. Pirkle, J. L. Distribution of the NHANES II lead subsample "weight" variable (April 11, 1983).

38. Pirkle, J. L. Appendix O: Propagation of error in calculating the percent decrease in blood lead levels over the NHANES II survey period (April 11, 1983).

39. Pirkle, J. L. Appendix P: Regressing ln (blood lead) on the demographic covariates and then regressing the residuals on GASQ compared to regressing ln (blood lead) simultaneously on the demographic covariates + GASQ (April 11, 1983).

40. Pirkle, J. L. Appendix Q: Regression of ln (blood lead) on the demographic covariates only and subsequently adding GASQ: F statistics, R square and Mallows $C_{(p)}$ (April 11, 1983).

Appendix D3

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†attended March 30-31 meeting only.

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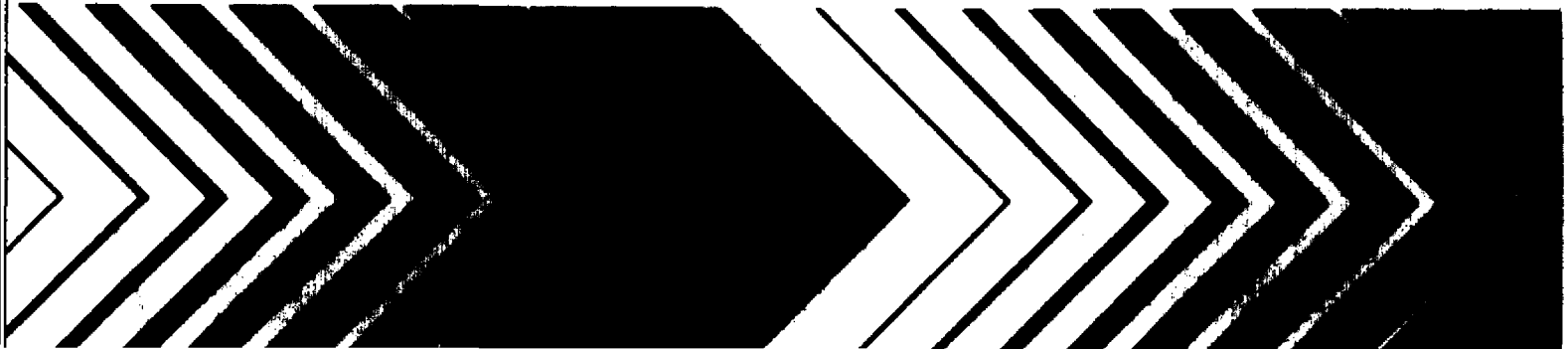

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Volume IV

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Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

ABSTRACT

The document evaluates and assesses scientific information on the health and welfare effects associated with exposure to various concentrations of lead in ambient air. The literature through 1983 has been reviewed thoroughly for information relevant to air quality criteria, although the document is not intended as a complete and detailed review of all literature pertaining to lead. An attempt has been made to identify the major discrepancies in our current knowledge and understanding of the effects of these pollutants.

Although this document is principally concerned with the health and welfare effects of lead, other scientific data are presented and evaluated in order to provide a better understanding of this pollutant in the environment. To this end, the document includes chapters that discuss the chemistry and physics of the pollutant; analytical techniques; sources, and types of emissions; environmental concentrations and exposure levels; atmospheric chemistry and dispersion modeling; effects on vegetation; and respiratory, physiological, toxicological, clinical, and epidemiological aspects of human exposure.

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LIST OF ABBREVIATIONS

AAS	Atomic absorption spectrometry
Ach	Acetylcholine
ACTH	Adrenocoticotrophic hormone
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADP/O ratio	Adenosine diphosphate/oxygen ratio
AIDS	Acquired immune deficiency syndrome
AIHA	American Industrial Hygiene Association
AII	Angiotensin II
ALA	Aminolevulinic acid
ALA-D	Aminolevulinic acid dehydrase
ALA-S	Aminolevulinic acid synthetase
ALA-U	Aminolevulinic acid in urine
APDC	Ammonium pyrrolidine-dithiocarbamate
APHA	American Public Health Association
ASTM	Amercian Society for Testing and Materials
ASV	Anodic stripping voltammetry
ATP	Adenosine triphosphate
B-cells	Bone marrow-derived lymphocytes
Ba	Barium
BAL	British anti-Lewisite (AKA dimercaprol)
BAP	benzo(a)pyrene
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
BW	Body weight
C.V.	Coefficient of variation
CaBP	Calcium binding protein
CaEDTA	Calcium ethylenediaminetetraacetate
CBD	Central business district
Cd	Cadmium
CDC	Centers for Disease Control
CEC	Cation exchange capacity
CEH	Center for Environmental Health
CFR	reference method
CMP	Cytidine monophosphate
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CP-U	Urinary coproporphyrin
C_{Cu}^{Pah}	plasma clearance of p-aminohippuric acid Copper
D.F.	Degrees of freedom
DA	Dopamine
DCMU	[3-(3,4-dichlorophenyl)-1,1-dimethylurea
DDP	Differential pulse polarography
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
EEC	European Economic Community
EEG	Electroencephalogram
EMC	Encephalomyocarditis
EP	Erythrocyte protoporphyrin
EPA	U.S. Environmental Protection Agency

LIST OF ABBREVIATIONS (continued).

FA	Fulvic acid
FDA	Food and Drug Administration
Fe	Iron
FEP	Free erythrocyte protoporphyrin
FY	Fiscal year
G.M.	Grand mean
G-6-PD	Glucose-6-phosphate dehydrogenase
GABA	Gamma-aminobutyric acid
GALT	Gut-associated lymphoid tissue
GC	Gas chromatography
GFR	Glomerular filtration rate
HA	Humic acid
Hg	Mercury
hi-vol	High-volume air sampler
HPLC	High-performance liquid chromatography
i.m.	Intramuscular (method of injection)
i.p.	Intraperitoneally (method of injection)
i.v.	Intravenously (method of injection)
IAA	Indol-3-ylacetic acid
IARC	International Agency for Research on Cancer
ICD	International classification of diseases
ICP	Inductively coupled plasma
IDMS	Isotope dilution mass spectrometry
IF	Interferon
ILE	Isotopic Lead Experiment (Italy)
IRPC	International Radiological Protection Commission
K	Potassium
LAI	Leaf area index
LDH-X	Lactate dehydrogenase isoenzyme x
LC_{50}	Lethyl concentration (50 percent)
LD_{50}	Lethal dose (50 percent)
LH_{50}	Luteinizing hormone
LIPO	Laboratory Improvement Program Office
ln	National logarithm
LPS	Lipopolysaccharide
LRT	Long range transport
mRNA	Messenger ribonucleic acid
ME	Mercaptoethanol
MEPP	Miniature end-plate potential
MES	Maximal electroshock seizure
MeV	Mega-electron volts
MLC	Mixed lymphocyte culture
MMD	Mass median diameter
MMED	Mass median equivalent diameter
Mn	Manganese
MND	Motor neuron disease
MSV	Moloney sarcoma virus
MTD	Maximum tolerated dose
n	Number of subjects
N/A	Not Available

LIST OF ABBREVIATIONS

NA	Not Applicable
NAAQS	National ambient air quality standards
NADB	National Aerometric Data Bank
NAMS	National Air Monitoring Station
NAS	National Academy of Sciences
NASN	National Air Surveillance Network
NBS	National Bureau of Standards
NE	Norepinephrine
NFAN	National Filter Analysis Network
NFR-82	Nutrition Foundation Report of 1982
NHANES II	National Health Assessment and Nutritional Evaluation Survey II
Ni	Nickel
OSHA	Occupational Safety and Health Administration
P	Potassium
p	Significance symbol
PAH	Para-aminohippuric acid
Pb	Lead
PBA	Air lead
$Pb(Ac)_2$	Lead acetate
PbB	concentration of lead in blood
PbBrCl	Lead (II) bromochloride
PBG	Porphobilinogen
PFC	Plaque-forming cells
pH	Measure of acidity
PHA	Phytohemagglutinin
PHZ	Polyacrylamide-hydrous-zirconia
PIXE	Proton-induced X-ray emissions
PMN	Polymorphonuclear leukocytes
PND	Post-natal day
PNS	Peripheral nervous system
ppm	Parts per million
PRA	Plasma renin activity
PRS	Plasma renin substrate
PWM	Pokeweed mitogen
Py-5-N	Pyrimide-5'-nucleotidase
RBC	Red blood cell; erythrocyte
RBF	Renal blood flow
RCR	Respiratory control ratios/rates
redox	Oxidation-reduction potential
RES	Reticuloendothelial system
RLV	Rauscher leukemia virus
RNA	Ribonucleic acid
S-HT	Serotonin
SA-7	Simian adenovirus
scm	Standard cubic meter
S.D.	Standard deviation
SDS	Sodium dodecyl sulfate
S.E.M.	Standard error of the mean
SES	Socioeconomic status
SGOT	Serum glutamic oxaloacetic transaminase

LIST OF ABBREVIATIONS (continued).

sIg	Surface immunoglobulin
SLAMS	State and local air monitoring stations
SMR	Standardized mortality ratio
Sr	Strontium
SRBC	Sheep red blood cells
SRMs	Standard reference materials
STEL	Short-term exposure limit
SW voltage	Slow-wave voltage
T-cells	Thymus-derived lymphocytes
t-tests	Tests of significance
TBL	Tri-n-butyl lead
TEA	Tetraethyl-ammonium
TEL	Tetraethyllead
TIBC	Total iron binding capacity
TML	Tetramethyllead
TMLC	Tetramethyllead chloride
TSH	Thyroid-stimulating hormone
TSP	Total suspended particulate
U.K.	United Kingdom
UMP	Uridine monophosphate
USPHS	U.S. Public Health Service
VA	Veterans Administration
V_d	Deposition velocity
VER	Visual evoked response
WHO	World Health Organization
XRF	X-Ray fluorescence
X^2	Chi squared
Zn	Zinc
ZPP	Erythrocyte zinc protoporphyrin

MEASUREMENT ABBREVIATIONS

dl	deciliter
ft	feet
g	gram
g/gal	gram/gallon
g/ha·mo	gram/hectare·month
km/hr	kilometer/hour
l/min	liter/minute
mg/km	milligram/kilometer
$\mu g/m^3$	microgram/cubic meter
mm	millimeter
µmol	micrometer
ng/cm^2	nanograms/square centimeter
nm	namometer
nM	nanomole
sec	second

Chapter 12: Biological Effects of Lead Exposure

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Chapter 13: Risk Assessment

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12. BIOLOGICAL EFFECTS OF LEAD EXPOSURE

12.1 INTRODUCTION

As noted in Chapter 2, air quality criteria documents evaluate scientific knowledge of relationships between pollutant concentrations and their effects on the environment and public health. Early chapters of this document (Chapters 3-7) discuss: physical and chemical properties of lead; measurement methods for lead in environmental media; sources of emissions; transport, transformation, and fate; and ambient concentrations and other aspects of the exposure of the U.S. population to lead in the environment. Chapter 8 evaluates the projected impact of lead on ecosystems. Chapters 9-11, immediately proceeding this one, discuss: measurement techniques for lead in biologic media; aspects related to the uptake, distribution, toxicokinetics, and excretion of lead; and the relationship of various external and internal lead exposure indices to each other. This chapter assesses information regarding biological effects of lead exposure, with emphasis on (1) the qualitative characterization of various lead-induced effects and (2) the delineation of dose-effect relationships for key effects most likely of health concern at ambient exposure levels presently encountered by the general population of the United States.

In discussing biological effects of lead, one should note at the outset that, to date, lead has not been demonstrated to have any beneficial biological effect in humans. Some investigators have hypothesized that lead may serve as an essential element in certain mammalian species (e.g., the rat) and have reported experimental data interpreted as supporting such an hypothesis. However, a critical evaluation of these studies presented in Appendix 12-A of this chapter raises serious questions regarding interpretation of the reported findings; and the subject studies are currently undergoing intensive evaluation by an expert committee convened by EPA. Therefore, pending the final report from that expert committee, the present chapter does not address the issue of potential essentiality of lead.

It is clear from the evidence evaluated in this chapter that there exists a continuum of biological effects associated with lead across a broad range of exposure. At rather low levels of lead exposure, biochemical changes, e.g., disruption of certain enzymatic activities involved in heme biosynthesis and erythropoietic pyrimidine metabolism, are detectable. With increasing lead exposure, there are sequentially more pronounced effects on heme synthesis and a broadening of lead effects to additional biochemical and physiological mechanisms in various tissues, such that increasingly more severe disruption of the normal functioning of many different organ systems becomes apparent. In addition to impairment of heme biosynthesis, signs of disruption of normal functioning of the erythropoietic and nervous systems are among the earliest effects observed in response to increasing lead exposure. At increasingly higher exposure levels, more severe disruption of the erythropoietic and nervous systems occurs; and

other organ systems are also affected so as to result in the manifestation of renal effects, disruption of reproductive functions, impairment of immunological functions, and many other biological effects. At sufficiently high levels of exposure, the damage to the nervous system and other effects can be severe enough to result in death or, in some cases of non-fatal lead poisoning, long-lasting sequelae such as permanent mental retardation.

The etiologies of many of the different types of functional disruption of various mammalian organ systems derive (at least in their earliest stages) from lead effects on certain subcellular organelles, which result in biochemical derangements (e.g., disruption of heme synthesis processes) common to and affecting many tissues and organ systems. Some major effects of lead on subcellular organelles common to numerous organ systems in mammalian species are discussed below in Section 12.2, with particular emphasis on lead effects on mitochondrial functions. Subsequent sections of the chapter discuss biological effects of lead in terms of various organ systems affected by that element and its compounds (except for Section 12.7, which assesses genotoxic and carcinogenic effects of lead). Additional cellular and subcellular aspects of the biological effects of lead are discussed within respective sections on particular organ systems.

Sections 12.3 to 12.9 have been sequenced generally according to the degree of known vulnerability of each organ system to lead. Major emphasis is placed first on discusssion of the three systems classically considered to be most sensitive to lead (i.e., the hematopoietic, the nervous, and the renal systems). The next sections then discuss the effects of lead on reproduction and development (in view of the impact of lead on the fetus and pregnant women), as well as gametotoxic effects of lead. Genotoxic effects of lead and evidence for possible carcinogenic effects of lead are then reviewed, followed by discussion of lead effects on the immune system and, lastly, other organ systems.

This chapter is subdivided mainly according to organ systems to facilitate presentation of information. It must be noted, however, that, in reality, all systems function in delicate concert to preserve the physiological integrity of the whole organism and all systems are interdependent. Thus, not only do effects in a critical organ often exert impacts on other organ systems, but low-level effects that might be construed as unimportant in a single specific system may be of concern in terms of their cumulative or aggregate impact.

Special emphasis is placed on the discussion of lead exposure effects in children. They are particularly at risk due to sources of exposure, mode of entry, rate of absorption and retention, and partitioning of lead in soft and hard tissues. The greater sensitivity of children to lead toxicity, their inability to recognize symptoms, and their dependence on parents and health care professionals all make them an especially vulnerable population requiring special consideration in developing criteria and standards for lead.

12.2 SUBCELLULAR EFFECTS OF LEAD IN HUMANS AND EXPERIMENTAL ANIMALS

The biochemical or molecular basis for lead toxicity is the ability of the toxicant, as a metallic cation, to bind to ligating groups in biomolecular substances crucial to normal physiological functions, thereby interfering with these functions via such mechanisms as competition with native essential metals for binding sites, inhibition of enzyme activity, and inhibition or other alterations of essential ion transport. The relationship of this basis for lead toxicity to organ- and organelle-specific effects is modulated by: (1) the inherent stability of such binding sites for lead; (2) the compartmentalization kinetics governing lead distribution among body compartments, among tissues, and within cells; and (3) differences in biochemical and physiological organization across tissues and cells due to their specific function. Given complexities introduced by factors 2 and 3, it is not surprising that no single, unifying mechanism of lead toxicity has been demonstrated to apply across all tissues and organ systems.

In the 1977 Air Quality Criteria Document for Lead, cellular and subcellular effects of lead were discussed, including effects on various classes of enzymes. Much of the literature detailing the effects of lead on enzymes *per se* has entailed study of relatively pure enzymes *in vitro* in the presence of added lead. This was the case for data discussed in the earlier document and such information continues to appear in the literature. Much of this material is of questionable relevance for effects of lead *in vivo*. On the other hand, lead effects on certain enzymes or enzyme systems are recognized as integral mechanisms of action underlying the impact of lead on tissues *in vivo* and are logically discussed in later sections below on effects at the organ system level.

This subsection is mainly concerned with organellar effects of lead, especially those that provide some rationale for lead toxicity at higher levels of biological organization. While a common mechanism at the subcellular level that would account for all aspects of lead toxicity has not been identified, one fairly common cellular response to lead is the impairment of mitochondrial structure and function; thus, mitochondrion effects are accorded major attention here. Lead effects on other organelles have not been as extensively studied as mitochondrion effects; and, in some cases, it is not clear how the available information, e.g., that on lead-containing nuclear inclusion bodies, relates to organellar dysfunction.

12.2.1 Effects of Lead on the Mitochondrion

The mitochondrion is clearly the target organelle for toxic effects of lead on many tissues, the characteristics of vulnerability varying somewhat with cell type. Given early recognition of this sensitivity, it is not surprising that an extensive body of *in vivo* and *in vitro* data has accumulated, which can be characterized as evidence of: (1) structural injury to the mitochondrion; (2) impairment of basic cellular energetics and other mitochondrial functions; and (3) uptake of lead by mitochondria *in vivo* and *in vitro*.

12.2.1.1 Lead Effects on Mitochondrial Structure. Changes in mitochondrial morphology with lead exposure have been well documented in humans and experimental animals and, in the case of the kidney, are a rather early response to such exposure. Earlier studies have been reviewed by Goyer and Rhyne (1973), followed by later updates by Fowler (1978) and Bull (1980).

Chronic oral exposure of adult rats to lead (1 percent lead acetate in diet) results in structural changes in renal tubule mitochondria, including swelling with distortion or loss of cristae (Goyer, 1968). Such changes have also been documented in renal biopsy tissue of lead workers (Wedeen et al., 1975; Biagini et al., 1977) and in tissues other than kidney, i.e., heart (Malpass et al., 1971; Moore et al., 1975b), liver (Hoffman et al., 1972), and the central (Press, 1977) and peripheral (Brashear et al., 1978) nervous systems.

While it appears that relatively high level lead exposures are necessary to detect structural changes in mitochondria in some animal models (Goyer, 1968; Hoffman et al., 1972), changes in rat heart mitochondria have been seen at blood lead levels as low as 42 µg/dl. Also, in the study of Fowler et al. (1980), swollen mitochondria or renal tubule cells were seen in rats chronically exposed to lead from gestation to 9 months of age at a dietary lead dosing level as low as 50 ppm and a median blood lead level of 26 µg/dl (range 15-41 µg/dl). Taken collectively, these differences point out relative tissue sensitivity, dosing protocol, and the possible effect of developmental status (Fowler et al., 1980) as important factors in determining lead exposure levels at which mitochondria are affected in various tissues.

12.2.1.2 Lead Effects on Mitochondrial Function. Both in vivo and in vitro studies dealing with such effects of lead as the impact on energy metabolism, intermediary metabolism, and intracellular ion transport have been carried out in various experimental animal models. Of particular interest for this section are such effects of lead in the developing versus the adult animal, given the greater sensitivity of the young organism to lead.

12.2.1.3 In Vivo Studies. Uncoupled energy metabolism, inhibited cellular respiration using succinate and NAD-linked substrates, and altered kinetics of intracellular calcium have all been documented for animals exposed to lead in vivo, as reviewed by Bull (1980).

Adult rat kidney mitochondria, following chronic oral feeding of lead in the diet (1 percent lead acetate, 10 or more weeks) showed a marked sensitivity of the pyruvate-NAD reductase system (Goyer, 1971), as indicated by impairment of pyruvate-dependent respiration indexed by ADP/O ratio and respiratory control rates (RCRs). Succinate-mediated respiration in these animals, however, was not different from controls. In contrast, Fowler et al. (1980) found in rats exposed in utero (dams fed 50 or 250 ppm lead) and for 9 months postnatally (50 or 250 ppm lead in their diet) renal tubule mitochondria that exhibited decreased state 3 respiration and RCRs for both succinate and pyruvate/malate substrates. This may have been due to longer exposure to lead or a differential effect of lead exposure during early development.

Intraperitoneal administration of lead to adult rats at doses as low as 12 mg/kg over 14 days was associated with inhibition of potassium-stimulated respiration in cerebral cortex slices with impairment of NAD(P)H oxidation using glucose but not pyruvate as substrate (Bull et al., 1975). This effect occurred at a corresponding blood lead of 72 µg/dl and a brain lead content of 0.4 µg/g, values below those associated with overt neurotoxicity. Bull (1977), in a later study, demonstrated that the respiratory response of cerebral cortical tissue from lead-dosed rats receiving a total of 60 mg Pb/kg (10 mg/kg x 6 dosings) over 14 days was associated with a marked decrease in turnover of intracellular calcium in a cellular compartment that appears to be the mitochondrion. This is consistent with the observation of Bouldin et al. (1975) that lead treatment leads to increased retention of calcium in guinea pig brain.

Numerous studies have evaluated relative effects of lead on mitochonodria of developing vs. adult animals, particularly in the nervous system. Holtzman and Shen Hsu (1976) exposed rat pups at 14 days of age to lead via milk of mothers fed lead in the diet (4 percent lead carbonate) with exposure lasting for 14 days. A 40 percent increase in state 4 respiratory rate of cerebellar mitochonodria was seen within one day of treatment and was lost at the end of the exposure period. However, at this later time (28 days of age), a substantial inhibition of state 3 respiration was observed. This early effect of lead on uncoupling oxidative phosphorylation is consistent with the results of Bull et al. (1979) and McCauley et al. (1979). In these investigations, female rats received lead in drinking water (200 ppm) from 14 days before breeding through weaning of the pups. At 15 days of age, cerebral cortical slices showed alteration of potassium-stimulated respiratory response and glucose uptake.

Holtzman et al. (1980a) compared mitochondrial respiration in cerebellum and cerebrum in rat pups exposed to lead beginning at 14 days of age (via milk of mothers fed 4 percent lead carbonate) and in adult rats maintained on the same diet. Cerebellar mitochondria showed a very early loss (by 2 days of exposure) of respiratory control in the pups with inhibition of phosphorylation-coupled respiration for NAD-linked substrates but not for succinate. Such changes were less pronounced in mitochondria of the cerebrum and were not seen for either brain region in the adult rat. This regional and age dependency of mitochondrial impairment parallels features of lead encephalopathy.

In a second study addressing this issue, Holtzman et al. (1981) measured the cytochrome contents of cerebral and cerebellar mitochondria from rat pups exposed either from birth or at 14 days of age via the same dosing protocol noted above. These were compared to adult animals exposed in like fashion. Pups exposed to lead from birth showed statistically significant reductions of cytochrome b, cytochromes c + c_1, and cytochromes a + a_3 in cerebellum by 4 weeks of exposure. Changes in cerebral cytochromes, in contrast, were marginal. When lead exposure began at 14 days of age, little effect was observed, and adult rats showed little

change. This study indicates that the most vulnerable period for lead effects on developing brain oxidative metabolism is the same period where a major burst in such activity begins.

Related to effects of lead on energy metabolism in the developing animal mitochondrion is the effect on brain development. In the study of Bull et al. (1979) noted earlier, cerebral cytochrome c + c_1 levels between 10 and 15 days of age decreased in a dose-dependent fashion at all maternal dosing levels (5-100 mg Pb/liter drinking water) and corresponding blood lead values for the rat pups (11.7-35.7 µg/dl). Delays in synaptic development in these pups also occurred, as indexed by synaptic counts taken in the parietal cortex. As the authors concluded, uncoupling of energy metabolism appears to be causally related to delays in cerebral cortical development.

Consistent with the effects of lead on mitochondrial structure and function are in vivo data demonstrating the selective accumulation of lead in mitochondria. Studies in rats using radioisotopic tracers ^{210}Pb (Castallino and Aloj, 1969) and ^{203}Pb (Barltrop et al., 1971) demonstrate that mitochondria will accumulate lead in significant relative amounts, the nature of the accumulation seeming to vary with the dosing protocol. Sabbioni and Marafante (1976) as well as Murakami and Hurosawa (1973) also found that lead is selectively lodged in mitochondria. Of interest in regard to the effects of lead on brain mitochondria are the data of Moore et al. (1975a) showing uptake of lead by guinea pig cerebral mitochondria, and the results of Krigman et al. (1974c) demonstrating that mitochondria in brain from 6-month-old rats exposed chronically to lead since birth showed the highest uptake of lead (34 percent), followed by the nuclear fraction (31 percent). While the possibility of translocation of lead during subcellular fractionation can be raised, the distribution pattern seen in the reports of Barltrop et al. (1971) and Castallino and Aloj (1969) over multiple time points make this unlikely. Also, findings of in vivo uptake of lead in brain mitochondria are supported by in vitro data discussed below.

12.2.1.4 In Vitro Studies. In vitro studies of both the response of mitochondrial function to lead and its accumulation by the organelle have been reported, using both isolated mitochondria and tissues. Bull (1980) reviewed such data published up to 1979.

Significant reductions in mitochondrial respiration, using both NAD-linked and succinate substrates have been reported for isolated heart and brain mitochondria. The lowest levels of lead associated with such effects appear to be 5 µM or, in some cases, less. Available evidence suggests that the sensitive site for lead in isolated mitochondria is before cytochrome b in the oxidative chain and involves either tricarboxylic acid enzymes or non-heme protein/ubiquinone steps. If substrate specificity is compared, e.g., succinate vs. glutamate/malate oxidation, there appear to be organ-specific differences. As Bull (1980) noted, tissue-specific effects of lead on cellular energetics may be one bases for differences in toxicity across organs. Also, several enzymes involved in intermediary metabolism in isolated mito-

chondria have been observed to undergo significant inhibition in activity in the presence of lead, and these have been tabulated by Bull (1980).

One focus of studies dealing with lead effects on isolated mitochondria has been ion transport--particularly that of calcium. Scott et al. (1971) have shown that lead movement into rat heart mitochondria involves active transport, with characteristics similar to those of calcium, thereby establishing a competitive relationship. Similarly, lead uptake into brain mitochondria is also energy dependent (Holtzman et al., 1977; Goldstein et al., 1977). The recent elegant studies of Pounds and coworkers (Pounds et al., 1982a,b), using labeled calcium or lead and desaturation kinetic studies of these labels in isolated rat hepatocytes, have elucidated the intracellular relationship of lead to calcium in terms of cellular compartmentalization. In the presence of graded amounts of lead (10, 50, or 100 μM), the kinetic analysis of desaturation curves of calcium-45 label showed a lead dose-dependent increase in the size of all three calcium compartments within the hepatocyte, particularly that deep compartment associated with the mitochondrion (Pounds et al., 1982a). Such changes were seen to be relatively independent of serum calcium or endogenous regulators of systemic calcium metabolism. Similarly, the use of lead-210 label and analogous kinetic analysis (Pounds et al., 1982b) showed the same three compartments of intracellular distribution as noted for calcium, including the deep component (which has the mitochondrion). Hence, there is striking overlap in the cellular metabolism of calcium and lead. These studies not only further confirm easy entry of lead into cells and cellular compartments, but also provide a basis for perturbation by lead of intracellular ion transport, particularly in neural cell mitochondria, where there is a high capability for calcium transport. Such capability is approximately 20-fold higher than in heart mitochondria (Nicholls, 1978).

Given the above observations, it is not surprising that a number of investigators have noted the *in vitro* uptake of lead into isolated mitochondria. Walton (1973) noted that lead is accumulated within isolated rat liver mitochondria over the range of 0.2-100 μM lead; and Walton and Buckley (1977) extended this observation to mitochondria in rat kidney cells in culture. Electron microprobe analyses of isolated rat synaptosomes (Silbergeld et al., 1977) and capillaries (Silbergeld et al., 1980b) incubated with lead ion have established that significant accumulation of lead, along with calcium, occurs in the mitochondrion. These observations are consistent with the kinetic studies of Pounds et al. (1982a,b), and the *in vitro* data for isolated capillaries are in accord with the observations of Toews et al. (1978), who found significant lead accumulation in brain capillaries of the suckling rat.

12.2.2 Effects of Lead on the Nucleus

With lead exposure, a cellular reaction typical of many species (including humans) is the formation of intranuclear lead-containing inclusion bodies, early data for which have been sum-

marized by Goyer and Moore (1974). In brief, these lead-bearing inclusion bodies: (1) have been verified as to lead content by X-ray microanalysis (Carroll et al., 1970); (2) consist of a rather dense core encapsulated by a fibrillary envelope; (3) are a complex of lead and the acid fractions of nuclear protein; (4) can be disaggregated in vitro by EDTA; (5) can appear very rapidly after lead exposure (Choie et al., 1975); (6) consist of a protein moiety in the complex which is synthesized de novo; and (7) have been postulated to serve a protective role in the cell, given the relative amounts of lead accumulated and presumably rendered toxicologically inert.

Based on renal biopsy studies, Cramer et al. (1974) concluded that such inclusion body formation in renal tubule cells in lead workers is an early response to lead entering the kidney, in view of decreased presence as a function of increased period of employment. Schumann et al. (1980), however, observed a continued exfoliation of inclusion-bearing tubule cells into urine of workers having a variable employment history.

Any protective role played by the lead inclusion body appears to be an imperfect one, to the extent that both subcellular organelle injury and lead uptake occur simultaneously with such inclusion formation, often in association with severe toxicity at the organ system level. For example, Osheroff et al. (1982), observed lead inclusion bodies in the anterior horn cells of the cervical spinal cord and neurons of the substantia nigra (as well as in renal tubule cells) in the adult rhesus monkey, along with damage to the vascular walls and glial processes and ependymal cell degeneration. At the light- and electron-microscope level, there were no signs of neuronal damage or altered morphology except for the inclusions. As noted by the authors, these inclusions in the large neurons of the substantia nigra show that the neuron will take up and accumulate lead. In the study of Fowler et al. (1980), renal tubule inclusions were observed simultaneously with evidence of structural and functional damage to the mitochondrion, all at relatively low levels of lead. Hence, it appears that a limited protective role for these inclusions may extend across a range of lead exposure.

Chromosomal effects and other indices of genotoxicity in humans and animals are discussed in Section 12.7 of this chapter.

12.2.3 Effects of Lead on Membranes

In theory, the cell membrane is the first organelle to encounter lead, and it is not surprising that cellular effects can be ascribed to interactions at cellular and intracellular membranes, mainly appearing to be associated with ion transport processes across membranes. In Section 12.3 a more detailed discussion is accorded the effects of lead on the membrane as they relate to the erythrocyte in terms of increased cell fragility and increased osmotic resistance. These effects can be rationalized, in large part, by the documented inhibition by lead of erythrocyte membrane (Na^+, K^+)-ATPase.

Lead also appears to interfere with the normal processes of calcium transport across membranes of various tissue types. Silbergeld and Adler (1978) have described lead-induced retardation of the release of the neurotransmitter, acetylcholine, in peripheral cholinergic synaptosomes, due to a blockade of calcium binding to the synaptosomal membrane reducing calcium-dependent choline uptake and subsequent release of acetylcholine from the nerve terminal. Calcium efflux from neurons is mediated by the membrane (Na^+, K^+)-ATPase via an exchange process with sodium. Inhibition of the enzyme by lead, as also occurs with the erythroctye (see above), increases the concentration of calcium within nerve endings (Goddard and Robinson, 1976). As seen from the data of Pounds et al. (1982a), lead can also elicit retention of calcium in neural cells by easy entry into the cell and by directly affecting the deep calcium compartment within the cell, of which the mitochondrion is a major component.

12.2.4 Other Organellar Effects of Lead

Studies of morphological alterations of renal tubule cells in the rat (Chang et al., 1981) and rabbit (Spit et al., 1981) with varying lead treatments have demonstrated lead-induced lysosomal changes. In the rabbit, with relatively modest levels of lead exposure (0.25 or 0.5 mg Pb/kg, 3 times weekly over 14 weeks) and corresponding blood lead values of 50 and 60 µg/dl, there was a dose-dependent increase in the amount of lysosomes in proximal convoluted tubule cells, as well as increased numbers of lysosomal inclusions. In the rat, exposure to 10 mg Pb/kg i.v. (daily over 4 weeks) resulted in the accumulation of lysosomes, some gigantic, in the pars recta segment of renal tubules. These animal data are consistent with observations made in lead workers (Cramer et al., 1974; Wedeen et al., 1975) and appear to represent a disturbance in normal lysosomal function, with the accumulation of lysosomes being due to enhanced degradation of proteins arising from effects of lead elsewhere within the cell.

12.2.5 Summary of Subcellular Effects of Lead

The biological basis of lead toxicity is closely linked to the ability of lead to bind to ligating groups in biomolecular substances crucial to normal physiological functions. This binding interferes with physiological processes by such mechanisms as: competition with native essential metals for binding sites; inhibition of enzyme activity; and inhibition or other changes in essential ion transport.

The main target organelle for lead toxicity in a variety of cell and tissue types clearly is the mitochondrion, followed probably by cellular and intracellular membranes. Mitochondrial effects take the form of structural changes and marked disturbances in mitochondrial function within the cell, especially energy metabolism and ion transport. These effects are

associated, in turn, with demonstrable accumulation of lead in mitochondria, both in vivo and in vitro. Structural changes include mitochondrial swelling in many cell types, as well as distortion and loss of cristae, which occur at relatively moderate levels of lead exposure. Similar changes have been documented in lead workers across a wide range of exposure levels.

Uncoupled energy metabolism, inhibited cellular respiration using both succinate and nicotinamide adenine dinucleotide (NAD)-linked substrates, and altered kinetics of intracellular calcium have been demonstrated in vivo using mitochondria of brain and non-neural tissue. In some cases, relatively moderate lead exposure levels have been associated with such changes, and several studies have documented the relatively greater sensitivity of this organelle in young versus adult animals in terms of mitochondrial respiration. The cerebellum appears to be particularly sensitive, providing a connection between mitochondrial impairment and lead encephalopathy. Impairment by lead of mitochondrial function in the developing brain has also been associated with delayed brain development, as indexed by content of various cytochromes. In the rat pup, ongoing lead exposure from birth is required for this effect to be expressed, indicating that such exposure must occur before, and is inhibitory to, the burst of oxidative metabolism activity that normally occurs in the young rat during 10 to 21 days postnatally.

In vivo lead exposure of adult rats has also been observed to markedly inhibit cerebral cortex intracellular calcium turnover (in a cellular compartment that appears to be the mitochondrion) at a brain lead level of 0.4 ppm. These results are consistent with a separate study showing increased retention of calcium in the brain of lead-dosed guinea pigs. A number of reports have described the in vivo accumulation of lead in mitochondria of kidney, liver, spleen, and brain tissue, with one study showing that such uptake was slightly more than occurred in the nucleus. These data are not only consistent with the various deleterious effects of lead on mitochondria but are also supported by other, in vitro findings.

Significant decreases in mitochondrial respiration in vitro using both NAD-linked and succinate substrates have been observed for brain and non-neural tissue mitochondria in the presence of lead at micromolar levels. There appears to be substrate specificity in the inhibition of respiration across different tissues, which may be a factor in differential organ toxicity. Also, a number of enzymes involved in intermediary metabolism in isolated mitochondria have been observed to undergo significant inhibition of activity with lead.

A major focus of research on lead effects on isolated mitochondria has concerned ion (especially calcuim) transport. Lead movement into brain and other tissue mitochondria, as does calcium movement, involves active transport. Recent sophisticated kinetic analyses of desaturation curves for radiolabeled lead or calcium indicate that there is striking overlap in the cellular metabolism of calcium and lead. These studies not only establish a basis for easy entry of lead into cells and cell compartments, but also provide a basis for impairment

by lead of intracellular ion transport, particularly in neural cell mitochondria, where the capacity for calcium transport is 20-fold higher than even in heart mitochondria.

Lead is also selectively taken up in isolated mitochondria in vitro, including the mitochondria of synaptosomes and brain capillaries. Given the diverse and extensive evidence of lead's impairment of mitochondrial structure and function as viewed from a subcellular level, it is not surprising that these derangements are logically held to be the basis of dysfunction of heme biosynthesis, erythropoiesis, and the central nervous system. Several key enzymes in the heme biosynthetic pathway are intramitochondrial, particularly ferrochelatase. Hence, it is to be expected that entry of lead into mitochondria will impair overall heme biosynthesis, and in fact this appears to be the case in the developing cerebellum. Furthermore, the levels of lead exposure associated with entry of lead into mitochondria and expression of mitochondrial injury can be relatively moderate.

Lead exposure provokes a typical cellular reaction in human and other species that has been morphologically characterized as a lead-containing nuclear inclusion body. Although it has been postulated that such inclusions constitute a cellular protection mechanism, such a mechanism is an imperfect one. Other organelles, e.g., the mitochondrion, also take up lead and sustain injury in the presence of nuclear inclusion bodies. Chromosomal effects and other indices of genotoxicity in humans and animals are considered later, in Section 12.7.

In theory, the cell membrane is the first organelle to encounter lead and it is not surprising that cellular effects of lead can be ascribed to interactions at cellular and intracellular membranes in the form of distrubed ion transport. The inhibition of membrane (Na^+,K^+)-ATPase of erythrocytes as a factor in lead-impaired erythropoiesis is noted elsewhere. Lead also appears to interfere with the normal processes of calcium transport across membranes of different tissues. In peripheral cholinergic synaptosomes, lead is associated with retarded release of acetylcholine owing to a blockade of calcium binding to the membrane, while calcium accumulation within nerve endings can be ascribed to inhibition of membrane (Na^+,K^+)-ATPase.

Lysosomes accumulate in renal proximal convoluted tubule cells of rats and rabbits given lead over a wide range of dosing. This also appears to occur in the kidneys of lead workers and seems to represent a disturbance in normal lysosomal function, with the accumulation of lysosomes being due to enhanced degradation of proteins because of the effects of lead elsewhere within the cell.

In so far as effects of lead on the activity of various enzymes are concerned, many of the available studies concern in vitro behavior of relatively pure enzymes with marginal relevance to various effects in vivo. On the other hand, certain enzymes are basic to the effects of lead at the organ or organ system level, and discussion is best reserved for such effects in ensuing sections of the document dealing with these systems.

12.3 EFFECTS OF LEAD ON HEME BIOSYNTHESIS AND ERYTHROPOIESIS/ERYTHROCYTE PHYSIOLOGY IN HUMANS AND ANIMALS

Lead has well-recognized effects not only on heme biosynthesis, a crucial process common to many organ systems, but also on erythropoiesis and erythrocyte physiology. This section is therefore divided for purposes of discussion into: (1) effects of lead on heme biosynthesis and (2) effects of lead on erythropoiesis and erythrocyte physiology. Discussion of the latter is further subdivided into effects of lead on hemoglobin production, cell morphology and survival, and erythropoietic nucleotide metabolism. The interrelationship of effects of lead on heme biosynthesis and neurotoxic effects of lead are discussed in a final subsection. Attention is accorded to discussion of effects of both inorganic lead and alkyl lead compounds used as gasoline additives.

12.3.1 Effects of Lead on Heme Biosynthesis

The effects of lead on heme biosynthesis are very well known because of both their prominence and the large number of studies of these effects in humans and experimental animals. In addition to being a constituent of hemoglobin, heme is a prosthetic group of a number of tissue hemoproteins having diverse functions, such as myoglobin, the P-450 component of the mixed function oxidase system, and the cytochromes of cellular energetics. Hence, any effects of lead on heme biosynthesis will, perforce, pose the potential for multi-organ toxicity.

At present, much of the available information concerning the effects of lead on heme biosynthesis have been obtained by measurements in blood, due in large part to the relative ease of assessing such effects via measurements in blood and in part to the fact that blood is the vehicle for movement of metabolites from other organ systems. On the other hand, a number of reports have been concerned with lead effects on heme biosynthesis in tissues such as kidney, liver, and brain. In the discussion below, various steps in the heme biosynthetic pathway affected by lead are discussed separately, with information describing erythropoietic effects usually appearing first, followed by studies involving other tissues.

The process of heme biosynthesis results in formation of the porphyrin, protoporphyrin IX, starting with glycine and succinyl-coenzyme A. It culminates with the insertion of iron at the center of the porphyrin ring. As may be noted in Figure 12-1, lead interferes with heme biosynthesis by disturbing the activity of three major enzymes: (1) it indirectly stimulates, by feedback derepression, the mitochondrial enzyme delta-aminolevulinic acid synthetase (ALA-S), which mediates the condensation of glycine and succinyl-coenzyme A to form delta-aminolevulinic acid (δ-ALA); (2) it directly inhibits the cytosolic enzyme delta-aminolevulinic acid dehydrase (ALA-D), which catalyzes the cyclocondensation of two units of ALA to porphobilinogen; (3) it disturbs the mitochondrial enzyme ferrochelatase, found in liver, bone

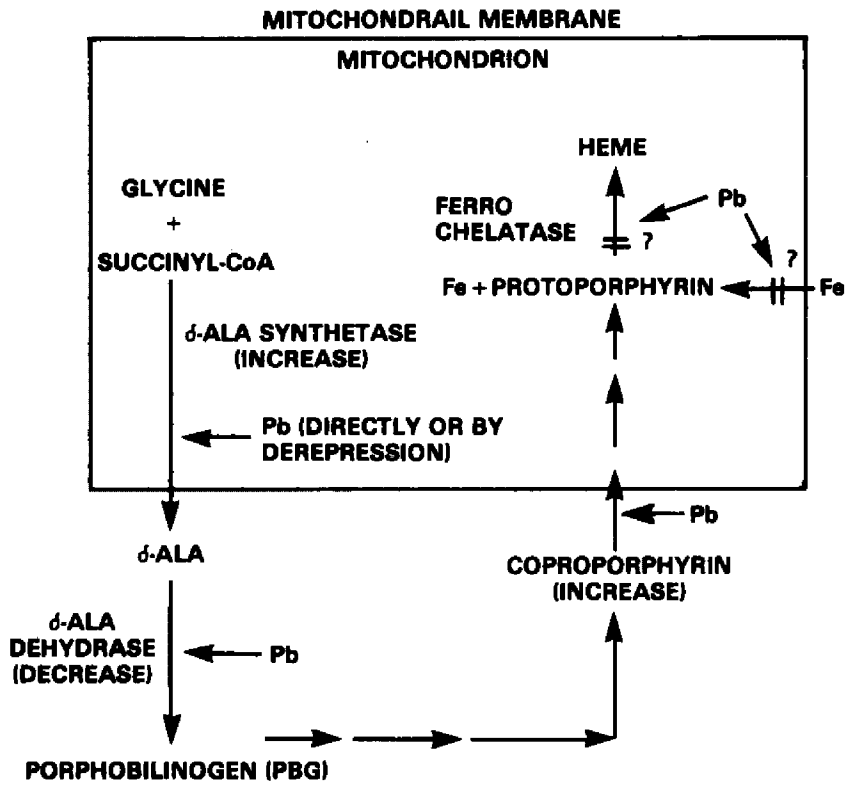

Figure 12-1. Lead effects on heme biosynthesis.

marrow, and other tissues, by either direct inhibition or alteration of intermitochondrial transport of iron ferrochelatase, which catalyzes the insertion of iron (II) into the protoporphyrin ring to form heme, the enzyme situated in mammals in the inner mitochondrial membrane (McKay et al., 1969).

12.3.1.1 Effects of Lead on δ-Aminolevulinic Acid Synthetase. The activity of the enzyme ALA-S is the rate-limiting step in the heme biosynthetic pathway. With decreased heme formation at other steps downstream or with increased heme oxygenase activity, compensatory increase of ALA-S activity occurs through feedback derepression and enhances the rate of heme formation. Hence, excess ALA formation is due to both stimulation of ALA-S and direct inhibition of ALA-D (see below).

Increased ALA-S activity has been reported in lead workers (Takaku et al., 1973; Campbell et al., 1977; Meredith et al., 1978), with leukocyte ALA-S stimulated at a blood lead value of 40 μg/dl (Meredith et al., 1978), a level at which ALA-D activity is significantly inhibited. To the extent that mitochondria in leukocytes show a dose-effect relationship comparable to the bone marrow and hepatic systems, it appears that most of the excess ALA formation below the observed threshold value is due to ALA-D inhibition. From the authors' data, blood ALA had increased about 2-fold in these workers over the blood lead range 18 μg/dl to 40 μg/dl.

In vitro and in vivo experimental data have provided mixed results in terms of the direction of the effect of lead on ALA-S activity. Silbergeld et al. (1982) observed that ALA-S activity was increased in kidney with acute lead exposure in rats, while chronic treatment was associated with increased activity of the enzyme in spleen. In liver, however, ALA-S activity was reduced under both acute and chronic dosing. Fowler et al. (1980) reported that renal ALA-S activity was significantly reduced in rats continuously exposed to lead in utero, through development, and up to 9 months of age. Meredith and Moore (1979) noted a steady increase in hepatic ALA-S activity when rats were given lead parenterally over an extended period of time. Maxwell and Meyer (1976) and Goldberg et al. (1978) also noted increased ALA-S activity in rats given lead parenterally. It appears that the type and time-frame of dosing influences the observed effect of lead on the enzyme activity. Using a rat liver cell line (RLC-GAI) in culture, Kusell et al. (1978) demonstrated that lead could produce a time-dependent increase in ALA-S activity. Stimulation of activity was observed at lead levels as low as 5×10^{-6} M, with maximum stimulation at 10^{-5} M. The authors report that the activity increase was associated with biosynthesis of more enzyme, rather than stimulation of the pre-existing enzyme. Lead-stimulated ALA-S formation was also not limited to liver cells; rat gliomas and mouse neuroblastomas showed similar results.

12.3.1.2 Effects of Lead on δ-Aminolevulinic Acid Dehydrase and ALA Accumulation/Excretion. Delta-aminolevulinic acid dehydrase (5-aminolevulinate hydrolase; porphobilinogen synthetase; E.C. 4.2.1.24; ALA-D) is a sulfhydryl, zinc-requiring allosteric enzyme in the heme biosynthetic pathway which catalyzes the conversion of two units of ALA to porphobilinogen. The enzyme's activity is very sensitive to inhibition by lead, the inhibition being reversed by reactivation of the sulfhydryl group with agents such as dithiothreitol (Granick et al., 1973), zinc (Finelli et al., 1975), or zinc plus glutathione (Mitchell et al., 1977).

The activity of ALA-D appears to be inhibited at virtually all blood lead levels studied so far, and any threshold for this effect remains to be identified (see discussion below). Dresner et al. (1982) found that ALA-D activity in rat bone marrow suspensions was significantly inhibited to 35 percent of control levels in the presence of 5×10^{-7} M (0.5 μM) lead. This potency, on a comparative molar basis, was unmatched by any other metals tested. Recently, Fujita et al. (1981) showed evidence of an increase in the amount of ALA-D in erythrocytes in lead-exposed rats, ascribed to an increased rate of ALA-D synthesis in bone marrow cells. Hence, the commonly observed net inhibition of activity occurs even in the face of an increase in ALA-D synthesis.

Hernberg and Nikkanen (1970) found that enzyme activity was correlated inversely with (logarithmic) blood lead values in a group of urban, non-exposed subjects. Enzyme activity inhibition was 50 percent at a blood lead level of 16 μg/dl. Other reports have confirmed

these observations across age groups and exposure categories (Alessio et al., 1976b; Roels et al., 1975b; Nieberg et al., 1974; Wada et al., 1973). A ratio of activated to inhibited enzyme activity (versus a single activity measurement, which does not accommodate intersubject genetic variability) measured against blood lead in children with values between 20 and 90 µg/dl was employed by Granick et al. (1973) to obtain an estimated threshold of 15 µg/dl for an effect of lead. On the other hand, Hernberg and Nikkanen (1970) observed no threshold in their subjects, all of whom were at or below 16 µg/dl. The lowest blood lead actually measured by Granick et al. (1973) was higher than the values measured by Hernberg and Nikkanen (1970).

Kuhnert et al. (1977) reported that ALA-D activity measures in erythrocytes from both pregnant women and cord blood of infants at delivery are correlated with the corresponding blood lead values, using the activated/inhibited activity ratio method of Granick et al. (1973). The correlation coefficient of activity with lead level was higher in fetal erythrocytes ($r = -0.58$, $p < 0.01$) than in the mothers ($r = -0.43$, $p < 0.01$). The mean inhibition level was 28 percent in mothers vs. 12 percent in the newborn. A study by Lauwerys et al. (1978) in 100 pairs of pregnant women and infant cord blood samples confirms this observation, i.e., for fetal blood $r = 0.67$ ($p < 0.001$) and for maternal blood $r = -0.56$ ($p < 0.001$).

While several factors other than lead may affect the activity of erythrocyte ALA-D, much of the available information suggests that most of these factors do not materially compromise the interpretation of the relationship between enzyme activity and lead or the use of this relationship for screening purposes. Border et al. (1976) questioned the reliability of ALA-D activity measurement in subjects concurrently exposed to both lead and zinc, since zinc also affects the activity of the enzyme. The data of Meredith and Moore (1980) refute this objection. In subjects without exposure, having serum zinc values of 80-120 µM, there was only a minor activating effect with increasing zinc when contrasted to the correlation of activity and blood lead in these same subjects. In workers exposed to both lead and zinc, serum zinc values were greater than in subjects with just lead exposure, but the mean level of enzyme activity was still much lower than in controls ($p < 0.001$).

The preceding discussion indicates that neither differences within the normal range of physiological zinc in humans nor combined excessive zinc and lead exposure in workers materially affects ALA-D activity. The obverse of this, lead exposure in the presence of zinc deficiency, is probably the more significant issue, but one that has not been well studied. Since ALA-D is a zinc-requiring enzyme, one would expect that optimal activity would be governed by in vivo zinc availability. Furthermore, zinc deficiency could potentially have a dual deleterious effect on ALA-D activity, first by reduced activity with reduced zinc availability and second, by enhanced lead absorption in the presence of zinc deficiency (see Section 10.5), the increased lead burden further inhibiting ALA-D activity.

The recent study of Roth and Kirchgessner (1981) indicates that ALA-D activity is significantly decreased in the presence of zinc deficiency. In zinc-deficient rats showing reduced serum and urinary zinc levels, the level of erythrocyte ALA-D activity was only 50 percent that of pair-fed controls, while urinary ALA was significantly elevated. Although these investigators did not measure blood lead in deficient and control animal groups, it would appear that the level of inhibition is more than could be accounted for just on the basis of increased lead absorption from diet. Given the available information documenting zinc deficiency in children (Section 10.5) as well as the animal study of Roth and Kirchgessner (1981), the relationship of lead, zinc deficiency, and ALA-D activity in young children merits further, careful study.

Moore and Meredith (1979) noted the effects of carbon monoxide on the activity of ALA-D, comparing moderate or heavy smokers with non-smokers. At the highest level of carboxyhemoglobin measured in their smoker groups, the depression of ALA-D activity was 2.1 percent. In these subjects, a significant inverse correlation of ALA-D activity and blood lead existed, but there was no significant correlation of such activity and blood carboxyhemoglobin levels.

While blood ethanol has been reported to affect ALA-D activity (Moore et al., 1971; Abdulla et al., 1976), its effect is significant only with intake corresponding to acute alcohol intoxication. Hence, relevance of this observation to screening is limited, particularly in children. The effect is reversible, declining with clearing of alcohol from the blood stream.

The inhibition of ALA-D activity in erythrocytes by lead apparently reflects a similar effect in other tissues. Secchi et al. (1974) observed that there was a clear correlation in 26 lead workers between hepatic and erythrocyte ALA-D activity as well as the expected inverse correlation between such activity and blood lead in the range 12-56 µg/dl. In suckling rats, Millar et al. (1970) noted decreased enzyme activity in brain and liver as well as red cells when lead was administered orally. In the study of Roels et al. (1977), tissue ALA-D changes were not observed when dams were administered 1, 10, or 100 ppm lead in drinking water. However, the recent report of Silbergeld et al. (1982) described moderate inhibition of ALA-D activity in brain and significant inhibition in kidney, liver, and spleen when adult rats were acutely exposed to lead given intraperitoneally; chronic exposure was associated with reduced activity in kidney, liver, and spleen. Gerber et al. (1978) found that neonatal mice exposed to lead from birth through 17 days of age at a level of 1.0 mg/ml in water showed significant decreases in brain ALA-D activity ($p < 0.01$) at all time points studied. These results support the data of Millar et al. (1970) for the suckling rat. In this study by Millar et al., rats exposed from birth through adulthood only showed significant decreases of brain ALA-D activity at 15 and 30 days, which also supports other data for the developing rodent. It would appear, therefore, that brain ALA-D activity is more sensitive to lead in the developing animal than in the adult.

The study of Dieter and Finley (1979) sheds light on the relative sensitivity of ALA-D activity in several regions of the brain and permits comparison of blood vs. brain ALA-D activity as a function of lead level. Mallard ducks given a single pellet of lead showed, by 4 weeks, 1 ppm lead in blood, 2.5 ppm lead in liver, and 0.5 ppm lead in brain. Cerebellar ALA-D activity was reduced by 50 percent at a lead level below 0.5 ppm; erythrocyte enzyme activity was lowered by 75 percent. Hepatic ALA-D activity was comparable to cerebellar activity or somewhat less, although the lead level in the liver was 5-fold higher. Cerebellar ALA-D activity was significantly below that for cerebrum. In an avian species, then, at blood lead levels where erythrocyte ALA-D activity is significantly depressed, activity of the enzyme in cerebellum was even more affected relative to lead concentration. The Roels et al. (1977) data may reflect a lower effective dose delivered to the rat pups in maternal milk as well as the dose taken in by the dams themselves, since they similarly showed no tissue enzyme activity changes.

The inhibition of ALA-D is reflected by increased levels of its substrate, ALA, in urine (Haeger, 1957) as well as in whole blood or plasma (Meredith et al., 1978; MacGee et al., 1977; Chisolm, 1968; Haeger-Aronsen, 1960). The detailed study of Meredith et al. (1978), which involved both control subjects and lead workers, indicated that in elevated lead exposure the increase in urinary ALA is preceded by a significant rise in circulating levels of ALA. The overall relationship of plasma ALA to blood lead was exponential and showed a perceptible continuation of an ALA-blood lead correlation into the control group to include the lowest value, 18 μg/dl. The relationship of plasma ALA to urinary levels of the precursor was found to be exponential, indicating that as plasma ALA increases, a greater proportion undergoes excretion into urine. Inspection of the plot of urinary vs. plasma ALA in these subjects shows that the correlation persists down to the plasma ALA concentration corresponding to the lowest blood lead level, 18 μg/dl. Cramer et al. (1974) have demonstrated that ALA clearance into urine parallels glomerular filtration rate across a range of lead exposures, suggesting that increased urinary output with increasing circulating ALA is associated with decreased tubular reabsorption (Moore et al., 1980). This study employed the method of Haeger-Aronsen (1960), which does not account for the presence of amino-acetone. If amino-acetone were interfering at low blood lead levels, however, one might expect an obliteration of the association, since this metabolite is not affected by lead exposure and its concentration should be randomly distributed in plasma and urine of the subjects.

Urinary ALA has been employed extensively as an indicator of excessive lead exposure, particularly in occupational settings (e.g., Davis et al., 1968; Selander and Cramér, 1970; Alessio et al., 1976a). The reliability of this test in initial screening of children for lead exposure has been questioned by Specter et al. (1971) and Blanksma et al. (1969), who

pointed out the failure of urinary ALA analysis to detect lead exposure when compared with blood lead values. This is due to the fact that an individual subject will show a wide variation in urinary ALA with random sampling. Chisolm et al. (1976) showed that reliable levels could only be obtained with 24-hour collections. In children with blood lead levels above 40 µg/dl the relationship of ALA in urine to blood lead becomes similar to that observed in lead workers (see below).

A correlation exists between blood lead and the logarithm of urinary ALA in workers (Meredith et al., 1978; Alessio et al., 1976a; Roels et al., 1975a; Wada et al., 1973; Selander and Cramér, 1970) and in children (National Academy of Sciences, 1972). Selander and Cramér (1970) reported that two different correlation curves were obtained, one for individuals below 40 µg/dl blood lead, and a different one for values above this, although the degree of correlation was less than with the entire group. A similar observation has been reported by Lauwerys et al. (1974) from a study of 167 workers (10-75 µg/dl). Meredith et al. (1978) found that the correlation curve for blood ALA vs. urinary ALA was linear below a blood lead of 40 µg/dl, as was the relationship of blood ALA to blood lead. Hence, there was also a linear relationship between blood lead and urinary ALA below 40 µg/dl, i.e., a continuation of the correlation below the commonly accepted threshold blood lead value of 40 µg/dl (see below). Tsuchiya et al. (1978) have questioned the relevance of using single correlation curves to describe the blood lead-urinary ALA relationship across a broad range of exposure, because they found that this relationship in workers showing moderate, intermediate, and high lead exposure could be described by three correlation curves of differing slope. This finding is consistent with the observations of Selander and Cramér (1970) as well as the results of Meredith et al. (1978) and Lauwerys et al. (1974). Chisolm et al. (1976) described an exponential correlation between blood lead and urinary ALA in children 5 years old or younger, with blood lead ranging from 25 to 75 µg/dl. In adolescents with blood lead below 40 µg/dl, no clear correlation was observed.

It is apparent from the above reports (Tsuchiya et al., 1978; Meredith et al., 1978; Selander and Cramér, 1970) that circulating ALA and urinary ALA are elevated and correlated at blood lead values below 40 µg/dl in humans. This is consistent, as in the Meredith et al. study, with the significant and steady increase in ALA-D inhibition concomitant with rising blood levels of ALA, even at blood lead values considerably below 40 µg/dl. Increases of ALA in tissues of experimental animals exposed to lead have also been documented. In the study of Silbergeld et al. (1982), acute administration of lead to adult rats was associated with an elevation in spleen and kidney ALA vs. that of controls, while in chronic exposure there was a moderate increase in ALA in the brain and a large increase (9-15 fold) in kidney and spleen. Liver levels with either form of exposure were not materially affected, although there was inhibition of liver ALA-D, particularly in the acute dose group.

12.3.1.3 Effects of Lead on Heme Formation from Protoporphyrin. The accumulation of protoporphyrin in the erythrocytes of individuals with lead intoxication has been recognized since the 1930s (Van den Bergh and Grotepass, 1933), but it has only recently been possible to study this effect through the development of sensitive and specific analytical techniques that permit quantitative measurement. In particular, the development of laboratory microtechniques and the hematofluorometer have allowed the determination of dose-effect relationships as well as the use of such measurements to screen for lead exposure.

In humans under normal circumstances, about 95 percent of the protoporphyrin in circulating erythrocytes is zinc protoporphyrin (ZPP) with the remaining 5 percent present as "free" protoporphyrin (Chisolm and Brown, 1979). Accumulation of protoporphyrin IX in the erythrocytes is the result of impaired iron (II) placement in the porphyrin moiety to form heme, an intramitochondrial process. In lead exposure, the porphyrin acquires a zinc ion, in lieu of the native iron, with the resulting ZPP tightly bound in the available heme pockets for the life of the erythrocyte, about 120 days (Lamola et al., 1975a,b).

In lead poisoning, the accumulation of protoporphyrin differs from that seen in the congenital disorder, erythropoietic protoporphyria. In the latter case, there is a defect in ferrochelatase function, leading to loose attachment of the porphyrin, accumulated without uptake of zinc, on the surface of the hemoglobin. Loose attachment permits diffusion into plasma and ultimately into the skin, where photosensitivity is induced. This behavior is absent in lead-associated porphyrin accumulation. The two forms of porphyrin, free and zinc-containing, differ sufficiently in fluorescence spectra to permit a laboratory distinction. With iron deficiency, there is also accumulation of protoporphyrin in the heme pocket as the zinc complex, resembling in large measure the characteristics of lead intoxication.

The elevation of erythrocyte ZPP has been extensively documented as being exponentially correlated with blood lead in children (Piomelli et al., 1973; Kammholz et al., 1972; Sassa et al., 1973; Lamola et al., 1975a,b; Roels et al., 1976) and in adult workers (Valentine et al., 1982; Lilis et al., 1978; Grandjean and Lintrup, 1978; Alessio et al., 1976b; Roels et al., 1975a, 1979; Lamola et al., 1975a,b). Reigart and Graber (1976) and Levi et al. (1976) have demonstrated that ZPP elevation can predict which children tend to increase their blood lead levels, a circumstance which probably rests on the nature of chronic lead exposure in certain groups of young children where a pulsatile blood lead curve is superimposed on some level of ongoing intake of lead which continues to elevate the ZPP values.

Accumulation of ZPP only occurs in erythrocytes formed during lead's presence in erythropoietic tissue, resulting in a lag of several weeks before the fraction of new ZPP-rich cells is large enough to influence total cell ZPP level. On the other hand, elevated ZPP in erythrocytes long after significant lead exposure has ceased appears to be a better indicator of

resorption of stored lead in bone than other measurements. Alessio et al. (1976b) reported that former lead workers, removed from exposure at the workplace for more than 12 months in all cases, still showed the typical logarithmic correlation with blood or urinary lead. However, the best correlation was observed between ZPP and chelatable lead, that fraction of total body burden considered toxicologically active (see Chapter 10). This post-exposure relationship for adults clearly indicates that significant levels of hematologically toxic lead continue to circulate long after exposure to lead has ceased.

In a report relevant to the problem of multi-indicator measurement to assess the degree of lead exposure, Hesley and Wimbish (1981) studied changes in blood lead and ZPP in two groups, newly exposed lead workers or those removed from significant exposure. In new workers, blood lead achieved a plateau at 9-10 weeks, while ZPP continued to rise over the entire study interval of 24 weeks. Among workers removed from exposure, both blood lead and ZPP values remained elevated up to the end of this study period (33 weeks), but the decline in ZPP concentration lagged behind blood lead in reaching a plateau. These investigators logically concluded that the difficulty in demonstrating reliable blood lead-ZPP relationships may reflect differences in when the two measures reach plateau. Similarly, more reliance should be placed on ZPP vs. blood lead levels before permitting re-entry into areas of elevated lead exposure.

The threshold for the effect of lead on ZPP accumulation is affected by the relative spread of blood lead values and the corresponding concentrations of ZPP. In many cases these range from "normal" levels in non-exposed subjects up to values reflecting considerable exposure. Furthermore, iron deficiency is also associated with ZPP elevation, particularly in children 2-3 years or younger.

In adults, Roels et al. (1975b) found that a cutoff for the relationship of erythrocyte protoporphyrin (EP) elevation to blood lead was 25-30 µg/dl, confirmed by the log-transformed data of Joselow and Flores (1977), Grandjean and Lintrup (1978), Odone et al. (1979), and Herber (1980).

In older children, 10-15 years of age, the data of Roels et al. (1976) indicate a threshold for effect of 15.5 µg/dl. The population dose-response relationship between EP and blood lead in these children indicated that EP levels were significantly higher (>2 SDs) than the reference mean in 50 percent of the children at a blood lead level of 25 µg/dl. In the age range of children studied here, iron deficiency is uncommon and these investigators did not note any significant hematocrit change in the exposure group. In fact, it was lower in the control group, although these subjects had lower ZPP levels. In this study, then, iron deficiency was unlikely to be a confounding factor in the primary relationship. Piomelli et al. (1977) obtained a comparable threshold value (15.5 µg/dl) for lead's effect on ZPP elevation

in children who were older than 4 years as well as those who were 2-4 years old. Were iron deficiency a factor in the results for this large study population (1816 children), one would expect a greater impact in the younger group, where the deficiency is more common.

Within the blood lead range considered "normal," i.e., below 30-40 µg/dl, assessment of any ZPP-blood lead relationship is strongly influenced by the relative analytical proficiency of the laboratory carrying out both measurements, particularly for blood lead at lower values. The type of statistical treatment of the data is also a factor, as are some biological sources of variability. With respect to subject variability, Grandjean (1979) has documented that ZPP increases throughout adulthood while hemoglobin remains relatively constant. Hence, age matching is a prerequisite. Similarly, the relative degree of ZPP response is sexually dichotomous, being greater in females for a given blood lead level (see discussion below).

Suga et al. (1981) claimed no apparent correlation between blood lead levels below 40 µg/dl and blood ZPP content in an adult population of 395 male and female subjects. The values for males and females were combined, based on no measured differences in ZPP response, which is at odds with the studies of Stuik (1974), Roels et al. (1975b), Zielhuis et al. (1978), Odone et al. (1978), and Toriumi and Kawai (1981). Also, EP was found to increase with increasing age, despite the fact that the finding of no correlation between blood lead and ZPP was based on a study population with all age groups combined.

Piomelli et al. (1982) investigated both the threshold for the effect of lead on ZPP accumulation and a dose-response relationship in 2004 children, 1852 of whom had blood lead values below 30 µg/dl. In this study, blood lead and EP measurements were done in facilities with a high proficiency for both blood lead and ZPP analyses. The study employed two statistical approaches (segmental line techniques and probit analysis), both of which revealed an average threshold blood lead level of 16.5 µg/dl in either the full group or the children with blood values below 30 µg/dl. In this report, the effect of iron deficiency and other non-lead factors was tested and removed using the Abbott formula (Abbott, 1925). With respect to population dose-response relationships, it was found that blood lead values corresponding to significant EP elevation at more than 1 or 2 standard deviations above a reference mean in 50 percent of the subjects were 28.6 or 35.6 µg/dl blood lead, respectively. At a blood lead level of 30 µg/dl, furthermore, it was determined that 27 percent of children would have an EP greater than 53 µg/dl.

Comparison of ZPP elevation among adult males and females and children at a given blood lead level generally indicates that children and adult females are more sensitive to this effect of lead. Lamola et al. (1975a,b) demonstrated that the slope of ZPP vs. blood lead was steeper in children than in adults. Roels et al. (1976) found that women and children were equally more sensitive in response than adult males, a finding also observed in the population

studied by Odone et al. (1979). Other comparisons between adults, either as groups studied at random or in a voluntary lead exposure study, also document the sensitivity of females vs. males to this effect of lead (Stuik, 1974; Roels et al., 1975b, 1976, 1979; Toriumi and Kawai, 1981). The heightened response of females to lead-associated EPP elevation was investigated in rats (Roels et al., 1978a) and shown to relate to hormonal interactions with lead, confirming the human data of Roels et al. (1975b, 1976, 1979) that iron status is not a factor in the phenomenon.

The effect of lead on iron incorporation into protoporphyrin in the heme biosynthetic pathway is not restricted to the erythropoietic system. Evidence of a generalized effect of lead on tissue heme synthesis at low levels of lead exposure comes from the recent studies of Rosen and coworkers (Rosen et al., 1980, 1981; Mahaffey et al., 1982). Children with blood lead levels in the range 12-120 μg/dl showed a strong negative correlation ($r = -0.88$) with serum 1,25-dihydroxy vitamin D ($1,25\text{-}(OH)_2D$). The slopes of the regression lines for subjects having blood lead below 30 μg/dl were not materially different from those over this level. Furthermore, when lead-intoxicated children were subjected to chelation therapy, it was observed that the depressed levels of serum $1,25\text{-}(OH)_2D$ returned to normal, while values of serum 25-hydroxy vitamin D (the precursor to $1,25\text{-}(OH)_2D$) remained the same. This indicates that lead has an inhibitory effect on renal 1-hydroxylase, a cytochrome P-450 mediated mitochondrial enzyme system that converts 25-(OH)D to $1,25\text{-}(OH)_2D$. The low end of the blood lead range associated with lowered $1,25\text{-}(OH)_2D$ levels and accompanying 1-hydroxylase activity inhibition corresponds to the lead level associated with the onset of EP accumulation in erythropoietic tissue (see above). Sensitivity of renal mitochondrial 1-hydroxylase activity to lead is consistent with a large body of information showing the susceptibility of renal tubule cell mitochondria to injury by lead and with the chronic lead exposure animal model of Fowler et al. (1980), discussed in more detail below.

Formation of the heme-containing protein cytochrome P-450, which is an integral part of the hepatic mixed function oxygenase system, has been documented as being affected by lead exposure, particularly acute lead intoxication, in animals (Alvares et al., 1972; Scappa et al., 1973; Chow and Cornish, 1978; Goldberg et al., 1978; Meredith and Moore, 1979) and humans (Alvares et al., 1975; Meredith et al., 1977; Fischbein et al., 1977). Many of these studies used altered drug detoxification rates as a functional measure of such effects. In the work of Goldberg et al. (1978), increasing level of lead exposure in rats was correlated with both steadily decreasing P-450 content of hepatic microsomes and decreased activity in the detoxifying enzymes aniline hydroxylase and aminopyrine demethylase, while the data of Meredith and Moore (1979) showed that continued dosing of rats with lead results in steadily decreased microsomal P-450 content, decreased total heme content of microsomes, and increased ALA-S activity.

Of interest in this regard are data relating to neural tissue. Studies of organotypic chick dorsal root ganglion in culture document that the nervous system has heme biosynthetic capability (Whetsell et al., 1978) and that this cell system, in the presence of lead, elaborates increased porphyrinic material (Sassa et al., 1979). Chronic administration of lead to neonatal rats indicates that at low levels of exposure, with modest elevations of blood lead, there is a retarded growth in the respiratory chain hemoprotein cytochrome C and disturbed electron transport function in the developing rat cerebral cortex (Holtzman and Shen Hsu, 1976; Bull et al., 1979). These effects on the developing organism are accentuated by increased whole body lead retention in both developing children and experimental animals, as well as by higher retention of lead in brain of suckling rats compared with adults (see Chapter 10).

Heme oxygenase activity is elevated in lead-intoxicated animals (Maines and Kappas, 1976; Meredith and Moore, 1979) in which relatively high dosing is employed, indicating that normal repression of this enzyme's activity is lost, further adding to heme reduction and loss of regulatory control on the heme biosynthetic pathway.

The mechanism(s) underlying derangement of heme biosynthesis leading to ZPP accumulaton in lead intoxication rests with either ferrochelatase inhibition, impaired mitochondrial transport of iron, or a combination of both. Inferentially, the resemblance of lead-associated ZPP accumulation to a similar effect of iron deficiency is consistent with the unavailability of iron to ferrochelatase rather than direct enzyme inhibition, while the porphyrin pattern seen in the congenital disorder, erythropoietic porphyria, where ferrochelatase itself is affected, is different from that seen in lead intoxication. Similarly, lead-induced effects on mitochondrial morphology and function are well known (Goyer and Rhyne, 1973; Fowler, 1978), and such disturbances may include impaired iron transport (Borová et al., 1973).

Several animal studies indicate that the effects of lead on heme formation may involve both ferrochelatase inhibition and impaired mitochondrial transport of iron. Hart et al. (1980) observed that acute lead exposure in rabbits is associated with a two-stage hematopoietic response, the earlier one resulting in significant formation of free vs. zinc protoporphyrin with considerable hemolysis, and a later phase (where ZPP is formed) which otherwise resembles the common features of lead intoxication. Subacute exposure shows more of the typical porphyrin response reported with lead. These data may suggest that acute lead poisoning is quite different from chronic exposure in terms of the nature of hematological derangement.

Fowler et al. (1980) maintained rats on a regimen of oral lead, starting with exposure of their dams to lead in water and continuing through 9 months after birth at levels up to 250 ppm lead. The authors observed that the activity of kidney mitochondrial ALA-S and ferro-

chelatase, but not that of the cytosolic enzyme ALA-D, was inhibited. Ferrochelatase activity was inhibited at 25, 50, and 250 ppm exposure levels, being 63 percent of the control values at the 250 ppm level. Depression of state-3 respiration control ratios was observed for both succinate and pyruvate. Ultrastructurally, the mitochondria were swollen and lysosomes were rich in iron. In this study, reduced ferrochelatase activity was observed while there was concomitant mitochondrial injury and disturbance of function. The accumulation of iron may be the result of phagocytized dead mitochondria or it may represent intracellular accumulation of iron owing to the inability of mitochondria to use the element. Ibrahim et al. (1979) have shown that excess intracellular iron under conditions of iron overload is stored in cytoplasmic lysosomes. The observation of disturbed mitochondrial respiration suggests, as do the mitochondrial function data of Holtzman and Shen Hsu (1976) and Bull et al. (1979) for the developing nervous system, that intramitochondrial transport of iron would be impaired. Flatmark and Romslo (1975) demonstrated that iron transport in mitochondria is energy linked and requires an intact respiration chain at the level of cytochrome C, whereby iron (III) on the C-side of the mitochondrial inner membrane is reduced before transport to the M-side and utilization in heme formation.

The above results are particularly interesting in terms of relative tissue response. While the kidney was affected, there was no change in blood indices of hematological derangement in terms of inhibited ALA-D activity or accumulation of ZPP. This suggests that there is a difference in dose-effect functions among different tissues, particularly with lead exposure during development of the organism. It appears that while indices of erythropoietic effects of lead may be more accessible, they may not be the most sensitive as indicators of heme biosynthesis derangement in other organs.

12.3.1.4 Other Heme-Related Effects of Lead. An increased excretion of coproporphyrin in the urine of lead workers and children with lead poisoning has long been recognized, and urinary coproporphyrin measurement has been used as an indicator of lead poisoning. The mechanism of such accumulation is not understood in terms of differentiating among direct enzyme inhibition, accumulation of substrate secondary to inhibition of heme formation, or impaired movement of the coproporphyrin intramitochondrially. Excess coproporphyrin excretion differs as an indicator of lead exposure from EP accumulation in that the former is a measure of ongoing lead intoxication without the lag in response seen with EP (Piomelli and Graziano, 1980).

In lead intoxication, there is an accumulation of porphobilinogen with elevated excretion in urine, owing to inhibition by lead of the enzyme uroporphyrinogen URO-I-synthetase (Piper and Tephly, 1974). In vitro studies of Piper and Tephly (1974) using rat and human erythrocyte and liver preparations indicate that it is the erythrocyte URO-I-synthetase in both rats and humans that is sensitive to the inhibitory effect of lead; activity of the hepatic enzyme

is relatively insensitive. Significant inhibition of the enzyme's activity occurs at 5 μM lead with virtually total inhibition of activity in human red cell hemolysates at 10^{-4} M. According to Piper and van Lier (1977), the lower sensitivity of hepatic URO-I-synthetase activity to lead is due to a protective effect afforded by a pteridine derivative, pteroylpolyglutamate. It appears that the protection does not occur through lead chelation, since hepatic ALA-D activity was reduced in the presence of lead. The studies of Piper and Tephly (1974) indicate that it is inhibition of URO-I-synthetase in erythroid tissue or erythrocytes that accounts for the accumulation of its substrate, porphobilinogen.

12.3.2 Effects of Lead on Erythropoiesis and Erythrocyte Physiology

12.3.2.1 Effects of Lead on Hemoglobin Production. Anemia is a manifestation (sometimes an early one) of chronic lead intoxication. Typically, the anemia is mildly hypochromic and usually normocytic. It is associated with reticulocytosis, owing to shortened cell survival, and the irregular presence of basophilic stippling. Its genesis lies in both decreased hemoglobin production and increased rate of erythrocyte destruction. Not only is anemia commonly seen in children with lead poisoning, but it appears to be more severe and frequent among those with severe lead intoxication (World Health Organization, 1977; National Academy of Sciences, 1972; Lin-Fu, 1973; Betts et al., 1973).

While the anemia associated with lead intoxication in children shows features of iron-deficiency anemia, there are differences in cases of severe intoxication. These differences include reticulocytosis, basophilic stippling, and a significantly lower total iron binding capacity (TIBC). These latter features suggest that iron-deficiency anemia in young children is exacerbated by lead. The reverse is also true.

In young children, iron deficiency occurs at a significant rate, based on national (Mahaffey and Michaelson, 1980) and regional (Owen and Lippman, 1977) surveys and is known to be correlated with increased lead absorption in humans (Yip et al., 1981; Chisolm, 1981; Watson et al., 1980; Szold, 1974; Watson et al., 1958) and animals (Hamilton, 1978; Barton et al., 1978; Mahaffey-Six and Goyer, 1972). Hence, prevalent iron deficiency can be seen to potentiate the effects of lead in reduction of hemoglobin by both increasing lead absorption and exacerbating the degree of anemia.

Also in young children, there is a negative correlation between hemoglobin level and blood lead levels (Adebonojo, 1974; Rosen et al., 1974; Betts et al., 1973; Puesche1 et al., 1972). These studies generally involved children under 6 years of age where iron deficiency may have been a factor. In adults, a negative correlation at blood lead values usually below 80 μg/dl has been observed (Grandjean, 1979; Lilis et al., 1978; Roels et al., 1975a; Wada, 1976), while several studies did not report any relationship below 80 μg/dl (Valentine et al.,

1982; Roels et al., 1979; Ramirez-Cervantes et al., 1978). In adults, iron deficiency would be expected to play less of a role in this relationship; Lilis et al. (1978) reported that the significant correlation between lead in blood and hemoglobin level was observed in workers where serum iron and TIBC were indistinguishable from controls.

The blood lead threshold for effects on hemoglobin has not been conclusively established. In children, this value appears to be about 40 µg/dl (World Health Organization, 1977), which is somewhat lower than in adults (Adebonojo, 1974; Rosen et al., 1974; Betts et al., 1973; Pueschel et al., 1972). Tola et al. (1973) observed no effect of lead on new workers until the blood lead had risen to a value of 50 µg/dl after about 100 days. The regression analysis data of Grandjean (1979), Lilis et al. (1978), and Wada (1976) show persistence of the negative correlation of blood lead and hemoglobin below 50 µg/dl. Human population dose-response data for the lead-hemoglobin relationship are limited. For lead workers, Baker et al. (1979) have calculated the corresponding dose-response (<14.0 g Hb/dl): 5 percent at blood lead of 40-59 µg/dl; 14 percent at blood lead of 60-79 µg/dl; and 36 percent at values above 80 µg/dl. In 202 lead workers, Grandjean (1979) noted the following percentage of workers having a hemoglobin level below 14.4 g/dl as a function of blood lead: <25 µg/dl, 17 percent; 25-60 µg/dl, 26 percent; >60 µg/dl, 45 percent.

The underlying mechanisms of lead-associated anemia appear to be a combination of reduced hemoglobin production and shortened erythrocyte survival because of direct cell damage. Effects of lead on hemoglobin production, furthermore, rest with disturbances of both heme and globin biosynthesis.

Biosynthesis of globin, the protein moiety of hemoglobin, also appears to be inhibited in lead exposure (Dresner et al., 1982; Wada et al., 1972; White and Harvey, 1972; Kassenaar et al., 1957). White and Harvey (1972) reported a decrease of globin synthesis in reticulocytes in vitro in the presence of lead at levels as low as 1.0 µM, corresponding to a blood lead level of 20 µg/dl. These data are in accord with the observation of Dresner et al. (1982), who noted a reduced globin synthesis (76 percent of controls) in rat bone marrow suspensions exposed to 1.0 µM lead. White and Harvey (1972) also noted that there was a decreased synthesis of alpha chains vs. beta chains.

Disturbance of globin biosynthesis is a consequence of lead's effects on heme formation since cellular heme regulates protein synthesis in erythroid cells (Levere and Granick, 1967) and regulates the translation of globin messenger RNA (Freedman and Rosman, 1976). The disturbance in the translation of mRNA in erythroid tissue may also reflect the effect of lead on pyrimidine metabolism.

12.3.2.2 Effects of Lead on Erythrocyte Morphology and Survival. It is clear that there is a hemolytic component to lead-induced anemia in humans owing to shortened erythrocyte survival,

and the various aspects of this effect have been reviewed by Waldron (1966), Goldberg (1968), Moore et al. (1980), Valentine and Paglia (1980), and Angle and McIntire (1982).

The relevant studies of shortened cell life with lead intoxication include observations of the behavior of red cells to mechanical and osmotic stress under in vivo and in vitro conditions. Waldron (1966) has discussed the frequent reports of increased mechanical fragility of erythrocytes from lead-poisoned workers, beginning with the work of Aub et al. (1926). Increased osmotic resistance of erythrocytes from subjects with lead intoxication is a parallel finding, both in vivo (Aub and Reznikoff, 1924; Harris and Greenberg, 1954; Horiguchi et al., 1974) and in vitro (Qazi et al., 1972; Waldron, 1964; Clarkson and Kench, 1956). Using an apparatus called a coil planet centrifuge, Karai et al. (1981) studied erythrocytes of lead workers and found significant increases in osmotic resistance; at the same time mean corpuscular volume and reticulocyte counts were not different from controls. Karai et al. suggest that one mechanism of increased resistance involves impairment of hepatic lecithin-cholesterol acyltransferase, leading to a build-up of cholesterol in the cell membrane. This resembles the increased osmotic resistance seen in obstructive jaundice where increased membrane cholesterol has been observed (Cooper et al., 1975). Karai et al. (1981) also reported an increased cholesterol-phospholipid ratio in lead workers' erythrocytes.

Erythrokinetic data in lead workers and children with lead-associated anemia have been reported. Shortening of erythrocyte survival has been demonstrated by Hernberg et al. (1967a) using tritium-labeled difluorophosphonate. Berk et al. (1970) used detailed isotope studies of a subject with severe lead intoxication to determine shorter erythrocyte life span, while Leiken and Eng (1963) observed shortened cell survival in three of seven children. These studies, as well as the reports of Landaw et al. (1973), White and Harvey (1972), Albaharry (1972), and Dagg et al. (1965), indicate that hemolysis is not the exclusive mechanism of anemia and that diminished erythrocyte production also plays a role.

The molecular basis for increased cell destruction with lead exposure includes the inhibition by lead of the activities of the enzymes (Na^+, K^+)-ATPase and pyrimidine-5'-nucleotidase. Erythrocyte membrane (Na^+, K^+)-ATPase is a sulfhydryl enzyme and inhibition of its activity by lead has been well documented (Raghavan et al., 1981; Secchi et al., 1968; Hasan et al., 1967; Hernberg et al., 1967b). In the study of Raghavan et al. (1981), enzyme activity was inversely correlated with membrane lead content ($p < 0.001$) in lead workers with or without symptoms of overt lead toxicity, while correlation with whole blood lead was poor. With enzyme inhibition, there is irreversible loss of potassium ion from the cell with undisturbed input of sodium into the cell, resulting in a relative increase in sodium. Since the cells "shrink," there is a net increase in sodium concentration, which likely results in increased mechanical fragility and cell lysis (Moore et al., 1980).

Both with lead exposure and in subjects with a genetic deficiency of the enzyme pyrimidine-5'-nucleotidase, activity is reduced, leading to impaired phosphorolysis of the nucleotides cytidine and uridine phosphate, which are then retained in the cell, causing interference with the conservation of the purine nucleotides necessary for cellular energetics (Angle and McIntire, 1982; Valentine and Paglia, 1980). A more detailed discussion of lead's interaction with this enzyme is presented in Section 12.3.2.3.

In a series of studies dealing with the hemolytic relationship of lead and vitamin E deficiency in animals, Levander et al. (1980) observed that lead exposure exacerbates the experimental hemolytic anemia associated with vitamin E deficiency by enhancing mechanical fragility, i.e., retarded cell deformability. These workers note that vitamin E deficiency is seen with children having elevated blood lead levels, especially subjects having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, indicating that the synergistic relationship seen in animals may exist in humans.

Glutathione is a necessary factor in erythrocyte function and structure. In workers exposed to lead, Roels et al. (1975a) found that there is a moderate but significant decrease in red cell glutathione compared with controls. This appears to reflect lead-induced impairment of glutathione synthesis.

12.3.2.3 Effects of Lead on Pyrimidine-5'-Nucleotidase Activity and Erythropoietic Pyrimidine Metabolism. The presence in lead intoxication of basophilic stippling and an anemia of hemolytic nature is similar to what is seen in subjects having a congenital deficiency of pyrimidine-5'-nucleotidase (Py-5-N), an enzyme mediating the phosphorolysis of the pyrimidine nucleotides, cytidine and uridine phosphates. With inhibition these nucleotides accumulate in the red cell or reticulocyte, there is a retardation of ribonuclease-mediated ribosomal RNA catabolism in maturing cells, and the resulting accumulation of aggregates of incompletely degraded ribosomal fragments accounts for the phenomenon of basophilic stippling.

In characterizing the enzyme Py-5-N, Paglia and Valentine (1975) observed that its activity was particularly sensitive to inhibition by certain metals, particularly lead, prompting further investigation of the interplay between lead intoxication and disturbances of erythropoietic pyrimidine metabolism. Paglia et al. (1975) observed that in subjects occupationally exposed to lead but having no evidence of basophilic stippling or significant frequency of anemia, the activity of Py-5-N was reduced to about 50 percent of control subjects and was most impaired in one worker with anemia, about 11 percent of normal. There was a general inverse correlation between enzyme activity and blood lead level. In this report, normal erythrocytes incubated with varying levels of lead showed detectable inhibition at levels as low as 0.1-1.0 μM, with consistent 50 percent inhibition at about 10 μM. Subsequently, these investigators (Valentine et al., 1976) observed that an individual with severe

lead intoxication had an 85 percent decrease in Py-5-N activity, basophilic stippling, and accumulation of pyrimidine nucleotides, mainly cytidine triphosphate. Since these parameters approached values seen in the congenital deficiency of Py-5-N, the data suggest a common etiology for the hemolytic anemia and stippling in both lead poisoning and the congenital disorder.

Several other reports of investigations of Py-5-N activity and pyrimidine nucleotide levels in lead workers have been published (Paglia et al., 1977; Buc and Kaplan, 1978). In nine workers having overt lead intoxication and blood lead values of 80-160 µg/dl, Py-5-N activity was significantly inhibited while the pyrimidine nucleotides comprised 70-80 percent of the total nucleotide pool, in contrast to trace levels in unexposed individuals (Paglia et al., 1977). In the study of Buc and Kaplan (1978), lead workers with or without overt lead intoxication all showed reduced activity of Py-5-N, which was inversely correlated with blood lead when the activity was expressed as a ratio with G-6-PD activity to accommodate an enhanced population of young cells due to hemolytic anemia. Enzyme inhibition was observed even when other indicators of lead exposure were negative.

Angle and McIntire (1978) observed that in 21 children 2-5 years old, with blood lead levels of 7-80 µg/dl, there was a negative linear correlation between Py-5-N activity and blood lead ($r = -0.60$, $p < 0.01$). Basophilic stippling was only seen in the child with the highest blood lead value and only two subjects had reticulocytosis. While adults tended to show a threshold for inhibition of Py-5-N at a blood lead level of 44 µg/dl or higher, there was no clear response threshold in these children. In a related investigation with 42 children 1-5 years old having blood lead levels of <10 to 72 µg/dl, Angle et al. (1982) noted that there was: (1) an inverse correlation ($r = -0.64$, $p < 0.001$) between the logarithm of Py-5-N activity and blood lead; (2) a positive log-log correlation between cytidine phosphates and blood lead in 15 of these children ($r = 0.89$, $p < 0.001$); and (3) an inverse relationship in 12 subjects between log of enzyme activity and cytidine phosphates ($r = -0.796$, $p < 0.001$). Study of the various relationships at low levels was made possible by the use of anion-exchange high performance liquid chromatography. In these studies, there was no threshold of effects of lead on either enzyme activity or cell nucleotide content even below 10 µg/dl. Finally, there was a significant positive correlation of pyrimidine nucleotide accumulation and the accumulation of ZPP.

In subjects undergoing therapeutic chelation with EDTA, Py-5-N activity increased, while there was no effect on pyrimidine nucleotides (Swanson et al., 1982), indicating that the pyrimidine accumulation is associated with the reticulocyte.

The metabolic significance of Py-5-N activity inhibition and nucleotide accumulation with lead exposure is derived from its effects on red cell membrane stability and survival by al-

teration of cellular energetics (Angle and McIntire, 1982), leading to cell lysis. A further consequence may be feedback inhibition of mRNA and protein synthesis, in that denatured mRNA may alter globin mRNA or globin chain synthesis. It was noted earlier that disturbances in heme production also affect the translation of globin mRNA (Freedman and Rosman, 1976). Hence, these two lead-associated disturbances of erythroid tissue function potentiate the effects of each other.

12.3.3 Effects of Alkyl Lead on Heme Synthesis and Erythropoiesis

In the Section 10.7 discussion of alkyl lead metabolism, it was noted that transformations of tetraethyl and tetramethyl lead in vivo result in generation not only of neurotoxic trialkyl lead metabolites but also of products of further dealkylation, including inorganic lead. One would therefore expect alkyl lead exposure to be associated with, in addition to other effects, some of those effects classically related to inorganic lead exposure.

Chronic gasoline sniffing has been recognized as a problem habit among children in rural or remote areas (Boeckx et al., 1977; Kaufman, 1973). When such practice involves leaded gasoline, the potential exists for lead intoxication. Boeckx et al. (1977) conducted surveys of children in remote Canadian communities in regard to the prevalence of gasoline sniffing and indications of chronic lead exposure. In one group of 43 children, all of whom sniffed gasoline, mean ALA-D activity was only 30 percent that of control subjects, with a significant correlation between the decrease in enzyme activity and the frequency of sniffing. A second survey of 50 children revealed similar results. Two children having acute lead intoxication associated with gasoline sniffing showed markedly lowered hemoglobin, elevated urinary ALA, and elevated urinary coproporphyrin. The authors estimated that more than half of disadvantaged children residing in rural or remote areas of Canada may have chronic lead exposure via this habit, consistent with the estimate of Kaufman (1973) of 62 percent for children in rural American Indian communities in the Southwest.

Robinson (1978) described two cases of pediatric lead poisoning due to habitual gasoline sniffing, one of which showed basophilic stippling. Hansen and Sharp (1978) reported that a young adult with acute lead poisioning due to chronic gasoline sniffing not only had basophilic stippling, but a 6-fold increase in urinary ALA, elevated urinary coproporphyrin, and an EP level about 4-fold above normal. In the reports of Boeckx et al. (1977) and Robinson (1978), increased lead levels were measured in urine in the course of chelation therapy, indicating that significant amounts of inorganic lead were present.

12.3.4 The Interrelationship of Lead Effects on Heme Synthesis and the Nervous System

Lead-associated disturbances in heme biosynthesis as a possible factor in the neurological effects of lead have been studied because of (1) the recognized similarity between

classic signs of lead neurotoxicity and many, but not all, of the neurological components of the congenital disorder, acute intermittent porphyria, and (2) some unusual aspects of lead neurotoxicity. Both acute attack porphyria and lead intoxication with neurological symptoms are variably accompanied by abdominal pain, constipation, vomiting, paralysis or paresis, demyelination, and psychiatric disturbances (Dagg et al., 1965; Moore et al., 1980; Silbergeld and Lamon, 1980). According to Angle and McIntire (1982), some of the unusual features of lead neurotoxicity are consistent with deranged hematopoiesis: (1) a lag in production of neurological symptoms; (2) the incongruity of early deficits in affective and cognitive function with the regional distribution of lead in the brain; and (3) a better correlation of neurobehavioral deficits with erythrocyte protoporphyrin than with blood lead. Item 3, it should be noted, is not universally the case (Hammond et al., 1980; Spivey et al., 1979).

While the nature and pattern of the derangements in heme biosynthesis in acute attack porphyria and lead intoxication differ in many respects, both involve excessive systemic accumulation and excretion of ALA, and this common feature has stimulated numerous studies of a connection between hemato- and neurotoxicity. In vitro data (Whetsell et al., 1978) have shown that the nervous system is capable of heme biosynthesis in the chick dorsal root ganglion. Sassa et al. (1979) found that the presence of lead in these preparations increases production of porphyrinic material, i.e., there is disturbed heme biosynthesis with accumulation of one or more porphyrins and, presumably, ALA. Millar et al. (1970) reported inhibited brain ALA-D activity in suckling rats exposed to lead, while Silbergeld et al. (1982) observed similar inhibition in brains of adult rats acutely exposed to lead. In the latter study, chronic lead exposure was also associated with a moderate increase in brain ALA without inhibition of ALA-D, suggesting an extra-neural source of the heme precursor. Moore and Meredith (1976) administered ALA to rats and observed that exogenous ALA can penetrate the blood-brain barrier. These reports suggest that ALA can either be generated in situ in the nervous system or can enter the nervous system from elsewhere.

Neurochemical investigations of ALA action in the nervous system have evaluated interactions with the neurotransmitter gamma-aminobutyric acid (GABA). Interference with GABAergic function by exposure to lead is compatible with such clinical and experimental signs of lead neurotoxicity as excitability, hyperactivity, hyperreactivity, and, in severe lead intoxication, convulsions (Silbergeld and Lamon, 1980). Of particular interest is the similarity in chemical structure between ALA and GABA, which differ only in that ALA has a carbonyl group on the alpha carbons, and GABA has a carbonyl group on the beta carbon.

While chronic lead exposure appears to alter neural pathways involving GABA function (Piepho et al., 1976; Silbergeld et al., 1979), this effect cannot be duplicated in vitro

using various levels of lead (Silbergeld et al., 1980). This suggests that lead does not impart the effect by direct interaction or an intact multi-pathway system is required. In vitro studies (Silbergeld et al., 1980a; Nicoll, 1976) demonstrate that ALA can displace GABA from synaptosomal membranes associated with synaptic function of the neurotransmitter on the GABA receptor, but that it is less potent than GABA by a factor of 10^3-10^4, suggesting that levels of ALA achieved even with severe intoxication may not be effectively competitive.

A more significant role for ALA in lead neurotoxicity may well be related to the observation that GABA release is subject to negative feedback control through presynaptic receptors on GABAergic terminals (Snodgrass, 1978; Mitchell and Martin, 1978). Brennan and Cantrill (1979) found that ALA inhibits K^+-stimulated release of GABA from pre-loaded synaptosomes by functioning as an agonist at the presynaptic receptors. The effect is evident at 21.0 μM ALA, while the inhibiting effect is abolished by the GABA antagonists bicuculline and picrotoxin. Of interest also is the demonstration (Silbergeld et al., 1980a) that synaptosomal release of preloaded ^{3}H-GABA, both resting and K^+-stimulated, is also inhibited in animals chronically treated with lead, paralleling the in vitro data of Brennan and Cantrill (1979) using ALA.

Silbergeld et al. (1982) described the comparative effects of lead and the agent succinylacetone, given acutely or chronically to adult rats, in terms of disturbances in heme synthesis and neurochemical indices. Succinylacetone, a metabolite that can be isolated from the urine of patients with hereditary tyrosinemia (Lindblad et al., 1977) is a potent inhibitor of heme synthesis, exerting its effect by ALA-D inhibition and derepression of ALA synthetase (Tschudy et al., 1980, 1983). Both agents, in vivo, showed significant inhibition of high affinity Na^+-dependent uptake of ^{14}C-GABA by cortex, caudate, and substantia nigra. However, neither agent affected GABA uptake in vitro. Similarly, both chronic or acute lead treatment and chronically administered succinylacetone reduced the seizure threshold to the GABA antagonist, picrotoxin. While these agents may involve entirely different mechanisms of toxicity to the GABAergic pathway, the fact remains that two distinct potent inhibitors of the heme biosynthetic pathway and ALA-D, which do not impart a common neurochemical effect by direct action on a neurotransmitter function, have a common neurochemical action in vivo.

Human data relating the hemato- and neurotoxicity of lead to each other are limited. Hammond et al. (1980) reported that the best correlates of the frequency of neurological symptoms in 28 lead workers were urinary and plasma ALA, which showed a higher correlation than EP. These data support a connection between heme biosynthesis impairment and neurological effects of ALA. Of interest here is the clinical report of Lamon et al. (1979) describing the effect of hematin [Fe(III)-heme] given parenterally to a subject with lead intoxication. Over the course of treatment (16 days), urinary coproporphyrin and ALA significantly dropped

and such neurological symptoms as lower extremity numbness and aching diminished. Blood lead levels were not altered during the treatment. Although remission of symptoms in this subject may have been spontaneous, the outcome parallels that observed in hematin treatment of subjects with acute porphyria in terms of similar reduction of heme indicators and relief of symptoms (Lamon et al., 1979).

Taken collectively, all of the available data strongly suggest that ALA, formed in situ or entering the brain, is neurotoxic to GABAergic function in particular. It inhibits K^+-stimulated GABA release by interaction with presynaptic receptors, where ALA appears to be particularly potent at very low levels, based on in vitro results. As described in the section on heme biosynthesis, lead can affect both cellular respiration and cytochrome C levels in the nervous system of the developing rat, which may contribute to manisfestation of some symptoms of lead neurotoxicity. Hence, more than the issue of ALA neurotoxicity should be considered in assessing connections between lead-induced hemato- and neurotoxicity.

12.3.5 Summary and Overview

12.3.5.1 Lead Effects on Heme Biosynthesis. Lead effects on heme biosynthesis are well known because of both their prominence and numerous studies of such effects in humans and experimental animals. The process of heme biosynthesis starts with glycine and succinyl-coenzyme A, proceeds through formation of protoporphyrin IX, and culminates with the insertion of divalent iron into the porphyrin ring, thus forming heme. In addition to being a constituent of hemoglobin, heme is the prosthetic group of many tissue hemoproteins having variable functions, such as myoglobin, the P-450 component of the mixed function oxygenase system, and the cytochromes of cellular energetics. Hence, disturbance of heme biosynthesis by lead poses the potential for multi-organ toxicity.

At present, steps in the heme synthesis pathway that have been best studied in regard to lead effects involve three enzymes: (1) stimulation of mitochondrial delta-aminolevulinic acid synthetase (ALA-S), which mediates formation of delta-aminolevulinic acid (ALA); (2) direct inhibition of the cytosolic enzyme, delta-aminolevulinic acid dehydrase (ALA-D), which catalyzes formation of porphobilinogen from two units of ALA; and (3) inhibition of insertion of iron (II) into protoporphyrin IX to form heme, a process mediated by ferrochelatase.

Increased ALA-S activity has been found in lead workers as well as lead-exposed animals, although the converse, an actual decrease in enzyme activity, has also been observed in several experimental studies using different exposure methods. It appears, then, that enzyme activity increase via feedback derepression or activity inhibition may depend on the nature of the exposure. Using rat liver cells in culture, ALA-S activity was stimulated in vitro at levels as low as 5.0 μM or 1.0 μg Pb/g preparation. The increased activity was seen to be due

to biosynthesis of more enzyme. The threshold for lead stimulation of ALA-S activity in humans, based on a study using leukocytes from lead workers, appears to be about 40 µg Pb/dl. The generality of this apparent threshold to other tissues depends on how well the sensitivity of leukocyte mitochondria mirrors that in other systems. The relative impact of ALA-S activity stimulation on ALA accumulation at lower lead exposure levels appears to be much less than the effect of ALA-D activity inhibition, to the extent that at ALA-D activity is significantly depressed at 40 µg/dl blood lead, where ALA-S activity only begins to be affected.

Erythrocyte ALA-D activity is very sensitive to lead inhibition, which is reversed by reactivation of the sulfhydryl group with agents such as dithiothreitol, zinc, or zinc plus glutathione. Zinc levels that achieve reactivation, however, are well above physiological levels. Although zinc appears to offset inhibitory effects of lead observed in human erythrocytes in vitro and in animal studies, lead workers exposed to both zinc and lead do not show significant changes in the relationship of ALA-D activity to blood lead compared with just lead exposure; nor does the range of physiological zinc in non-exposed subjects affect the activity. In contrast zinc deficiency in animals significantly inhibits activity, with concomitant accumulation of ALA in urine. Since zinc deficiency has also been demonstrated to increase lead absorption, the possibility exists for dual effects of such deficiency on ALA-D activity: (1) a direct effect on activity due to reduced zinc availability; and (2) increased lead absorption leading to further inhibition of activity.

Erythrocyte ALA-D activity appears to be inhibited at virtually all blood lead levels measured so far, and any threshold for this effect in either adults or children remains to be determined. A further measure of this enzyme's sensitivity to lead is a report that rat bone marrow suspensions show inhibition of ALA-D activity by lead at a level of 0.1 µg/g suspension. Inhibition of ALA-D activity in erythrocytes apparently reflects a similar effect in other tissues. Hepatic ALA-D activity was inversely correlated in lead workers with both erythrocyte activity as well as blood lead levels. Of significance are experimental animal data showing that (1) brain ALA-D activity is inhibited with lead exposure and (2) this inhibition appears to occur to a greater extent in developing vs. adult animals, presumably reflecting greater retention of lead in developing animals. In the avian brain, cerebellar ALA-D activity is affected to a greater extent than that of the cerebrum and, relative to lead concentration, shows inhibition approaching that occurring in erythrocytes.

Lead inhibition of ALA-D activity is reflected by elevated levels of its substrate, ALA, in blood, urine, and soft tissues. In one study, increases in urinary ALA were preceded by a rise in circulating levels of the metabolite. Blood ALA was elevated at all corresponding blood lead values down to the lowest determined (18 µg/dl), while urinary ALA increased exponentially with blood ALA.

Urinary ALA is employed extensively as an indicator of excessive lead exposure in lead workers. The value of this measurement in pediatric screening, however, is diagnostically limited if only spot urine collection is done, more satisfactory data being obtainable with 24-hour collections. Numerous independent studies document a direct correlation between blood lead and the logarithm of urinary ALA in human adults and children; the threshold for urinary ALA increases is commonly accepted as being 40 µg/dl. However, several studies of lead workers indicate that the correlation of urinary ALA with blood lead continues below this value, and one study found that the slope of the dose-effect curve in lead workers is dependent upon level of exposure.

The health significance of lead-inhibited ALA-D activity and accumulation of ALA at lower lead exposure levels is controversial, to the extent that the "reserve capacity" of ALA-D activity is such that only the level of inhibition associated with marked accumulation of the enzyme's substrate, ALA, in accessible indicator media may be significant. However, it is not possible to quantify, at lower levels of lead exposure, the relationship of urinary ALA to target tissue levels nor to relate the potential neurotoxicity of ALA at any accumulation level to levels in indicator media; i.e., the blood lead threshold for neurotoxicity of ALA may be different from that associated with increased urinary excretion of ALA.

Accumulation of protoporphyrin in erythrocytes of lead-intoxicated individuals has been recognized since the 1930s, but it has only recently been possible to quantitatively assess the nature of this effect via development of sensitive, specific microanalysis methods. Accumulation of protoporphyrin IX in erythrocytes results from impaired placement of iron (II) in the porphyrin moiety to form heme, an intramitochondrial process mediated by ferrochelatase. In lead exposure, the porphyrin acquires a zinc ion in lieu of native iron, thus forming zinc protoporphyrin (ZPP), and is tightly bound in available heme pockets for the life of the erythrocytes. This tight sequestration contrasts with the relatively mobile non-metal, or free, protoporphyrin (FEP) accumulated in the congenital disorder erythropoietic protoporphyria.

Elevation of erythrocyte ZPP has been extensively documented as being exponentially correlated with blood lead in children and adult lead workers and is presently considered one of the best indicators of undue lead exposure. Accumulation of ZPP only occurs in erythrocytes formed during lead's presence in erythroid tissue, resulting in a lag of at least several weeks before such build-up can be measured. The level of such accumulation in erythrocytes of newly employed lead workers continues to increase when blood lead has already reached a plateau. This influences the relative correlation of ZPP and blood lead in workers with short exposure histories. In individuals removed from occupational exposure, the ZPP level in blood declines much more slowly than blood lead, even years after removal from exposure or after a drop in blood lead. Hence, ZPP level appears to be a more reliable indicator of continuing intoxication from lead resorbed from bone.

The threshold for detection of lead-induced ZPP accumulation is affected by the relative spread of blood lead and corresponding ZPP values measured. In young children (< 4 yr old), the ZPP elevation associated with iron-deficiency anemia must also be considered. In adults, numerous studies indicate that the blood lead threshold for ZPP elevation is about 25-30 µg/dl. In children 10-15 years old, the threshold is about 16 µg/dl; in this age group, iron deficiency is not a factor. In one study, children over 4 years old showed the same threshold, 15.5 µg/dl, as a second group under 4 years old, indicating that iron deficiency was not a factor in the study. Fifty percent of the children had significantly elevated EP levels (2 standard deviations above reference mean EP) at 25 µg/dl blood lead.

At blood lead levels below 30-40 µg/dl, any assessment of the ZPP-blood lead relationship is strongly influenced by the relative analytical proficiency for measurement of both blood lead and EP. The types of statistical analyses used are also important. In a recent detailed statistical study involving 2004 children, 1852 of whom had blood lead values below 30 µg/dl, segmental line and probit analysis techniques were employed to assess the dose-effect threshold and dose-response relationship. An average blood lead threshold for the effect using both statistical techniques yielded a value of 16.5 µg/dl for either the full group or those subjects with blood lead below 30 µg/dl. The effect of iron deficiency was tested for and removed. Of particular interest was the finding that the blood lead values corresponding to EP elevations more than 1 or 2 standard deviations above the reference mean in 50 percent of the children were 28.6 or 35.7 µg Pb/dl, respectively. Hence, fully half of the children had significant elevations of EP at blood lead levels around 30 µg/dl, the currently accepted cut-off value for undue lead exposure. From various reports, children and adult females appear to be more sensitive to lead effects on EP accumulation at any given blood lead level, with children being somewhat more sensitive than adult females.

Lead effects on heme formation are not restricted to the erythropoietic system. Recent studies show that the reduction of serum $1,25\text{-}(OH)_2D$ seen with even low level lead exposure is apparently the result of lead inhibition of the activity of renal 1-hydroxylase, a cytochrome P-450 mediated enzyme. This heme-containing protein, cytochrome P-450 (an integral part of the hepatic mixed function oxygenase system), is affected in humans and animals by lead exposure, especially acute intoxication. Reduced P-450 content correlates with impaired activity of detoxifying enzyme systems such as aniline hydroxylase and aminopyrine demethylase.

Studies of organotypic chick dorsal root ganglion in culture show that the nervous system not only has heme biosynthetic capability but such preparations elaborate porphyrinic material in the presence of lead. In the neonatal rat, chronic lead exposure, resulting in moderately elevated blood lead, is associated with retarded increases in the hemoprotein, cytochrome C, and disturbed electron transport in the developing cerebral cortex. These data parallel effects of lead on ALA-D activity and ALA accumulation in neural tissue. When both these

effects are viewed in the toxicokinetic context of increased retention of lead in both developing animals and children, there is an obvious, serious potential for impaired heme-based metabolic function in the nervous system of lead-exposed children.

As can be concluded from the above discussion, the health significance of ZPP accumulation rests with the fact that it is evidence of impaired heme and hemoprotein formation in many tissues, arising from entry of lead into mitochondria. Such evidence for reduced heme synthesis is consistent with much data documenting lead-associated effects on mitochondria. The relative value of the lead-ZPP relationship in erythropoietic tissue as an index of this effect in other tissues hinges on the relative sensitivity of the erythropoietic system compared with other organ systems. One study of rats exposed to low levels of lead over their lifetime demonstrated that protoporphyrin accumulation in renal tissue was already significant at levels of lead exposure where little change was seen in erythrocyte porphyrin levels.

Other steps in the heme biosynthesis pathway are also known to be affected by lead, although these have not been as well studied on a biochemical or molecular level. Coproporphyrin levels are increased in urine, reflecting active lead intoxication. Lead also affects the activity of the enzyme uroporphyrinogen-I-synthetase, resulting in an accumulation of its substrate, porphobilinogen. The erythrocyte enzyme has been reported to be much more sensitive to lead than the hepatic species, presumably accounting for much of the accumulated substrate. Ferrochelatase is an intramitochondrial enzyme, and impairment of its activity, either directly by lead or via impairment of iron transport to the enzyme, is evidence of the presence of lead in mitochondria.

12.3.5.2 Lead Effects on Erythropoiesis and Erythrocyte Physiology. Anemia is a manifestation of chronic lead intoxication, being characterized as mildly hypochromic and usually normocytic. It is associated with reticulocytosis, owing to shortened cell survival, and the variable presence of basophilic stippling. Its occurrence is due to both decreased production and increased rate of destruction of erythrocytes. In young children (< 4 yr old) iron deficiency anemia is exacerbated by lead effects, and vice versa. Hemoglobin production is negatively correlated with blood lead in young children, where iron deficiency may be a confounding factor, as well as in lead workers. In one study, blood lead values that were usually below 80 µg/dl were inversely correlated with hemoglobin content. In these subjects, no iron deficiency was found. The blood lead threshold for reduced hemoglobin content is about 50 µg/dl in adult lead workers and somewhat lower (40 µg/dl) in children.

The mechanism of lead-associated anemia appears to be a combination of reduced hemoglobin production and shortened erythrocyte survival because of direct cell injury. Lead effects on hemoglobin production involve disturbances of both heme and globin biosynthesis. The hemolytic component to lead-induced anemia appears to be due to increased cell fragility and increased osmotic resistance. In one study using rats, the hemolysis associated with vitamin E

deficiency, via reduced cell deformability, was exacerbated by lead exposure. The molecular basis for increased cell destruction rests with inhibition of (Na^+, K^+)-ATPase and pyrimidine-5'-nucleotidase. Inhibition of the former enzyme leads to cell "shrinkage" and inhibition of the latter results in impaired pyrimidine nucleotide phosphorolysis and disturbance of the activity of the purine nucleotides necessary for cellular energetics.

12.3.5.3 Effects of Alkyl Lead Compounds on Heme Biosynthesis and Erythropoiesis. Tetraethyl lead and tetramethyl lead, components of leaded gasoline, undergo transformation in vivo to neurotoxic trialkyl metabolites as well as further conversion to inorganic lead. Hence, one might anticipate that exposure to such agents may show effects commonly associated with inorganic lead in terms of heme synthesis and erythropoiesis. Various surveys and case reports show that the habit of sniffing leaded gasoline is associated with chronic lead intoxication in children from socially deprived backgrounds in rural or remote areas. Notable in these subjects is evidence of impaired heme biosynthesis as indexed by significantly reduced ALA-D activity. In several case reports of frank lead toxicity from habitual leaded gasoline sniffing, effects such as basophilic stippling in erythrocytes and significantly reduced hemoglobin have also been noted.

12.3.5.4 Relationships of Lead Effects on Heme Synthesis to Neurotoxicity. The role of lead-associated disturbances of heme biosynthesis as a possible factor in neurological effects of lead is of considerable interest because of: (1) similarities between classical signs of lead neurotoxicity and several neurological components of the congenital disorder, acute intermittent porphyria; and (2) some of the unusual aspects of lead neurotoxicity. There are two possible points of connection between lead effects on heme biosynthesis and the nervous system. Associated with both lead neurotoxicity and acute intermittent porphyria is the common feature of excessive systemic accumulation and excretion of ALA. Secondly, lead neurotoxicity reflects, to some degree, impaired synthesis of heme and hemoproteins involved in crucial cellular functions. Available information indicates that ALA levels are elevated in the brain of lead-exposed animals, arising via in situ inhibition of brain ALA-D activity or via transport to the brain after formation in other tissues. ALA is known to traverse the blood-brain barrier. Hence, ALA is accessible to, or formed within, the brain during lead exposure and may express its neurotoxic potential.

Based on various in vitro and in vivo data obtained in the context of neurochemical studies of lead neurotoxicity, it appears that ALA can readily play a role in GABAergic function, particularly inhibiting release of the neurotransmitter GABA from presynaptic receptors, where ALA appears to be very potent even at low levels. In an in vitro study, agonist behavior by ALA was demonstrated at levels as low as 1.0 μM ALA. This in vitro observation supports results of a study using lead-exposed rats in which there was reported inhibition of

both resting and K^+-stimulated release of preloaded ^3H-GABA from nerve terminals. Further evidence for an effect of some agent other than lead acting directly is the observation that *in vivo* effects of lead on neurotransmitter function cannot be duplicated with *in vitro* preparations to which lead is added. Human data on lead-induced associations between disturbed heme synthesis and neurotoxicity, while limited, also suggest that ALA may function as a neurotoxicant.

The connection of impaired heme and hemoprotein synthesis in the neonatal rat brain was noted earlier, in terms of reduced cytochrome C production and impaired operation of the cytochrome C respiratory chain. Hence, one might expect that such impairment would be most prominent in areas of relatively greater cellularization, such as the hippocampus. As noted in Chapter 10, these are also regions where selective lead accumulation occurs.

12.4 NEUROTOXIC EFFECTS OF LEAD

12.4.1 Introduction

Historically, neurotoxic effects have long been recognized as being among the more severe consequences of human lead exposure (Tanqueral Des Planches, 1839; Stewart, 1895; Prendergast, 1910; Oliver, 1911; Blackfan, 1917). Since the early 1900's, extensive research has focused on the elucidation of lead exposure levels associated with the induction of various types of neurotoxic effects and related issues, e.g. critical exposure periods for their induction and their persistence or reversibility. Such research, spanning more than 50 years, has provided expanding evidence indicating that progressively lower lead exposure levels, previously accepted as "safe," are actually sufficient to cause notable neurotoxic effects of lead.

The neurotoxic effects of extremely high exposures resulting in blood lead levels in excess of 80-100 μg/dl, have been well documented--especially in regard to increased risk for fulminant lead encephalopathy (a well-known clinical syndrome characterized by overt symptoms such as gross ataxia, persistent vomiting, lethargy, stupor, convulsions, and coma of such severity that immediate medical attention is required). The persistence of neurological sequelae in cases of non-fatal lead encephalopathy has also been well established. The neurotoxic effects of subencephalopathic lead exposures in both human adults and children, however, continues to represent a major area of controversy and interest. Reflecting this, much research during the past 10-15 years has focussed on the delineation of exposure-effect relationships for: (1) the occurrence of overt signs and symptoms of neurotoxicity in relation to other indicators of subencephalopathic overt lead intoxication; and (2) the manifestation of more subtle, often difficult-to-detect indications of altered neurological functions in apparently asymptomatic (i.e., not overtly lead-poisoned) individuals.

The present assessment critically reviews the available scientific literature on the neurotoxic effects of lead, first evaluating the results of human studies bearing on the subject and then focusing on pertinent animal toxicology studies. The discussion of human studies is divided into two major subsections focusing on neurotoxic effects of lead exposure in (1) adults and (2) children. Both lead effects on the central nervous system (CNS) and the peripheral nervous system (PNS) are discussed in each case. In general, only relatively brief overview summaries are provided in regard to findings bearing on the effects of extremely high level exposures resulting in encephalopathy or other frank signs or symptoms of overt lead intoxication. Studies concerning the effects of lower level lead exposures are assessed in more detail, especially those dealing with non-overtly lead intoxicated children. As for the animal toxicology studies, particular emphasis is placed on the review of studies that help to address certain important issues raised by the human research findings, rather than attempting an exhaustive review of all animal toxicology studies concerning the neurotoxic effects of lead.

12.4.2 Human Studies

Defining exposure-effect or dose-response relationships between lead and particular neurotoxic responses in humans involves two basic steps. First, there must be an assessment of the internal lead burden resulting from external doses of lead received via various routes of exposure (such as air, water, food, occupational hazards, house dust, etc.). Internal lead burdens may be indexed by lead concentrations in blood, teeth, or other tissue, or by other biological indicators. The second step involves an assessment of the relationship of internal exposure indices to behavioral or other types of neurophysiological responses. The difficulty of this task is reflected by current controversies over existing data. Studies vary greatly in the quality of design, precision of assessment instruments, care in data collection, and appropriateness of statistical analyses employed. Many of these methodological problems are broadly common to research on toxic agents in general and not just to lead alone.

Although epidemiological studies of lead effects have immediate environmental relevance at the human level, difficult problems are often associated with the interpretation of the findings, as noted in several reviews (Bornschein et al., 1980; Cowan and Leviton, 1980; Rutter, 1980; Valciukas and Lilis, 1980; Neddleman and Landrigan, 1981. The main problems are: (1) inadequate markers of exposure to lead; (2) insensitive measures of performance; (3) bias in selection of subjects; (4) inadequate handling of confounding covariates; (5) inappropriate statistical analyses; (6) inappropriate generalization and interpretation of results; and (7) the need for "blind" evaluations by experimenters and technicians. Each of these problems are briefly discussed below.

Each major exposure route--food, water, air, dust, and soil--contributes to a person's total daily intake of lead (see Chapters 7 and 11 of this document). The relative contribution of each exposure route, however, is difficult to ascertain; neurotoxic endpoint measurements, therefore, are most typically evaluated in relation to one or another indicator of overall internal lead body burden. Subjects in epidemiological studies may be misclassified as to exposure level unless careful choices of exposure indices are made based upon the hypotheses to be tested, the accuracy and precision of the biological media assays, and the collection and assay procedures employed. Chapter 9 of this document evaluates different measures of internal exposure to lead and their respective advantages and disadvantages. The most commonly used measure of internal dose is blood lead concentration, which varies as a function of age, sex, race, geographic location, and exposure. The blood lead level is a useful marker of current exposure but generally does not reflect cumulative body lead burdens as well as lead levels in teeth. Hair lead levels, measured in some human studies, are not viewed as reliable indicators of internal body burdens at this time. Future research may identify a more standard exposure index, but it appears that a risk classification similar to

that of the U.S. Centers for Disease Control (1978) in terms of blood lead and FEP levels will continue in the foreseeable future to be the standard approach most often used for lead exposure screening and evaluation. Much of the discussion below is, therefore, focused on defining dose-effect relationships for human neurotoxic effects in terms of blood lead levels; some ancillary information on pertinent teeth lead levels is also discussed.

The frequency and timing of sampling for internal lead burdens represent another important factor in evaluating studies of lead effects on neurological and behavioral functions. For example, epidemiological studies often rely on blood lead and/or erythrocyte protoporphyrin (EP) levels determined at a single point in time to retrospectively estimate or characterize internal exposure histories of study populations that may have been exposed in the past to higher levels of lead than those indicated by a single current blood sample. Relatively few prospective studies exist that provide highly reliable estimates of critical lead exposure levels associated with observed neurotoxic effects in human adults or children, especially in regard to the effects of subencephalopathic lead exposures. Some prospective longitudinal studies on the effects of lead on early development of infants and young children (e.g., Bornschein, 1983) are currently in progress, but the results of these studies are not yet available. The present assessment of the neurotoxic effects of lead in humans must, therefore, rely heavily on published epidemiological studies which typically provide exposure history information of only limited value in defining exposure-effect relationships.

Key variables that have emerged in determining effects of lead on the nervous system include (1) duration and intensity of exposure and (2) age at exposure. Evidence suggest that young organisms with developing nervous systems are more vulnerable than adults with fully matured nervous systems. Particular attention is, therefore, accorded below to discussion of neurotoxic effects of lead in children as a special group at risk.

Precision of measurement is a critical methodological issue, especially when research on neurotoxicity leaves the laboratory setting. Neurotoxicity is often measured indirectly with psychometric or neurometric techniques in epidemiological studies (Valciukas and Lilis, 1980). The accuracy with which these tests reflect what they purport to measure (validity) and the degree to which they are reproducible (reliability) are issues central to the science of measurement theory. Many cross-sectional population studies make use of instruments that are only brief samples of behavior thought to be representative of some relatively constant underlying traits, such as intelligence. Standardization of tests is the subject of much research in psychometrics. The quality and precision of specific test batteries have been particularly controversial issues in evaluating possible effect levels for neurotoxic effects of lead exposure in children. Table 12B (Appendix 12B) lists some of the major tests used, together with their advantages and weaknesses. The following review places most weight on

results obtained with age-normed, standardized psychometric test instruments and well-controlled, standardized nerve conduction velocity (NCV) tests. Other measures, such as reaction time, finger tapping, and certain electrophysiological measures (e.g., cortical evoked and slow-wave potentials) are potentially more sensitive indices, but are still experimental measures whose clinical utility and psychometric properties with respect to the neurobehavioral toxicity of lead remain to be more fully explored.

Selection bias is a critical issue in epidemiological studies in which attempts are made to generalize from a small sample to a large population. Volunteering to participate in a study and attendance at special clinics or schools are common forms of selection bias that often limit how far the results of such studies can be generalized. These factors may need to be balanced in lead neurotoxicity research since reference groups are often difficult to find because of the pervasiveness of lead in the environment and the many non-lead covariates that also affect performance. Selection bias and the effects of confounding can be reduced by choosing a more homogeneous stratified sample, but the generalizability of the results of such cohort studies is thereby limited.

Perhaps the greatest methodological concern in epidemiological studies is controlling for confounding covariates, so that residual effects can be more confidently attributed to lead. Among adults, the most important covariates are age, sex, race, educational level, exposure history, alcohol intake, total food intake, dietary calcium and iron intake, and urban vs. rural styles of living (Valciukas and Lilis, 1980). Among children, a number of developmental covariates are additionally important: parental socioeconomic status (Needleman et al., 1979); maternal IQ (Perino and Ernhart, 1974); pica (Barltrop, 1966); quality of the caregiving environment (Hunt et al., 1982; Milar et al., 1980); dietary iron and calcium intake, vitamin D levels, body fat and nutrition (Mahaffey and Michaelson, 1980; Mahaffey, 1981); and age at exposure. Preschool children below the age of 3-5 years appear to be particularly vulnerable, in that the rate of accumulation of even a low body-lead burden is higher for them than for adults (National Academy of Sciences, Committee on Lead in the Human Environment, 1980). Potential confounding effects of covariates become particularly important when trying to interpret threshold effects of lead exposure. Each covariate alone may not be significant, but, when combined, may interact to pose a cumulative risk which could result in under- or overestimation of a small effect of lead.

Statistical considerations important not only to lead but to all epidemiological studies include adequate sample size (Hill, 1966), the use of multiple comparisons (Cohen and Cohen, 1975), and the use of multivariate analyses (Cooley and Lohnes, 1971). Regarding sample size, false negative conclusions are at times drawn from small studies with low statistical power. It is often difficult and expensive to use large sample sizes in complex research such as that

on lead neurotoxicity. This fact makes it all the more important to use sensitive assessment instruments which have a high level of discriminating power and can be combined into factors for multivariate analysis. Multiple statistical comparisons can then be made while reducing the likelihood of finding a certain number of significant differences by chance alone. This is a serious problem, because near-threshold effects are often small and variable.

A final crucial issue in this and other research revolves around the care taken to assure that investigators are isolated from information that might identify subjects in terms of their lead exposure levels at the time of assessment and data recording. Unconscious biases, nonrandom errors, and arbitrary data correction and exclusion can be ruled out only if a study is performed under blind conditions or, preferably, double-blind conditions.

With the above methodological considerations in mind, the following sections evaluate pertinent human studies, including an overview of lead exposure effects in adults, followed by a more detailed assessment of neurotoxic effects of lead exposures in children.

12.4.2.1 Neurotoxic Effects of Lead Exposures in Adults.

12.4.2.1.1 Overt lead intoxication in adults. Severe neurotoxic effects of extreme exposures to high levels of lead, especially for prolonged periods that produce overt signs of acute lead intoxication, are well documented in regard to both adults and children. The most profound (CNS) effects in adults have been referred to for many years as the clinical syndrome of lead encephalopathy, described in detail by Aub et al. (1926), Cantarow and Trumper (1944), Cumings (1959), and Teisinger and Stýblová (1961). Early features of the syndrome that may develop within weeks of initial exposure include dullness, restlessness, irritability, poor attention span, headaches, muscular tremor, hallucinations, and loss of memory. These symptoms may progress to delirium, mania, convulsions, paralysis, coma, and death. The onset of such symptoms can often be quite abrupt, with convulsions, coma, and even death occurring very rapidly in patients who shortly before appeared to exhibit much less severe or no symptoms of acute lead intoxication (Cumings, 1959; Smith et al., 1938). Symptoms of lead encephalopathy indicative of severe CNS damage and posing a threat to life are generally not seen in adults except at blood lead levels well in excess of 120 µg/dl (Kehoe, 1961a,b,c). Other data (Smith et al., 1938) suggest that acute lead intoxication, including severe gastrointestinal symptoms and/or signs of encephalopathy can occur in some adults at blood lead levels around 100 µg/dl, but ambiguities make this data difficult to interpret.

In addition to the above CNS effects, lead also clearly damages peripheral nerves at toxic, high exposure levels that predominantly affect large myelinated nerve fibers (Vasilescu, 1973; Feldman et al., 1977; Englert, 1980). Pathologic changes in peripheral nerves, as shown in animal studies, can include both segmental demyelination and, in some fibers, axonal degeneration (Fullerton, 1966). The former types of changes appear to reflect lead effects on

Schwann cells, with concomitant endoneurial edema and disruption of myelin membranes (Windebank and Dyck, 1981). Apparently lead induces a breakdown in the blood-nerve barrier which allows lead-rich edema fluid to enter the endoneurium (Dyck et al., 1980; Windebank et al., 1980). Remyelination observed in animal studies suggests either that such lead effects may be reversible or that not all Schwann cells are affected equally (Lampert and Schochet, 1968; Ohnishi and Dyck, 1981). Reports of plantar arch deformities due to old peripheral neuropathies (Emmerson, 1968), however, suggest that lead-induced neuropathies of sufficient severity in human adults could result in permanent peripheral nerve damage. Morphologically, peripheral neuropathies are usually detectable only after prolonged high exposure to lead, with distinctly different sensitivities and histological differences existing among mammalian species. In regard to man, as an example, Buchthal and Behse (1979, 1981), using nerve biopsies from a worker with frank lead neuropathy (blood lead = 150 µg/dl), found histological changes indicative of axonal degeneration in association in NCV reductions that corresponded to loss of large fibers and decreased amplitude of sensory potentials.

Data from certain studies provide a basis by which to estimate lead exposure levels at which adults exhibit overt signs or symptoms of neurotoxicity and to compare such levels with those associated with other types of signs and symptoms indicative of overt lead intoxication (Lilis et al., 1977; Irwig et al., 1978; Dahlgren et al., 1978; Baker et al., 1979; Hänninen et al., 1979; Spivey et al., 1979; Fischbein et al., 1980; Hammond et al., 1980). These studies evaluated the incidence of various clinical signs and symptoms of lead intoxication across a wide range of lead exposures among occupationally exposed smelter and battery plant workers. The reported incidences of particular types of signs and symptoms, both neurological and otherwise, and associated lead exposure levels varied considerably from study to study, but they collectively provide evidence indicating that overt neurological, gastrointestinal, and other lead-related symptoms can occur among adults starting at blood lead levels as low as 40-60 µg/dl. Considerable individual biological variability is apparent, however, among various study populations and individual workers in terms of observed lead levels associated with overt signs and symptoms of lead intoxication, based on comparisons of exposure-effect and dose-response data from the above studies. Irwig et al (1978), for example, report data for black South African lead workers indicative of clearly increased prevalence of both neurological and gastrointestinal symptoms at blood lead levels over 80 µg/dl. Analogously, Hammond et al. (1980) reported significant increases in neurological (both CNS and PNS) and gastrointestinal symptoms among American smelter workers with blood lead levels often exceeding 80 µg/dl, but not among workers whose exposure histories did not include levels above 80 µg/dl--findings in contrast to the results of several other studies. Lilis et al. (1977), for instance, found that CNS symptoms (tiredness, sleeplessness, irritability, headaches) were

reported by 55 percent and muscle or joint pain by 39 percent of a group of lead smelter workers whose blood lead levels had never been found to exceed 80 µg/dl. Low hemoglobin levels (<14g/dl) were found in more than 33 percent of these workers. Also, Spivey et al. (1977) reported significantly increased neurological (mainly CNS, but some PNS) symptoms and joint pain among a group of 69 lead workers with mean ± standard deviation blood lead levels of 61.3 ± 12.8 µg/dl in comparison to a control group with 22.0 ± 5.9 µg/dl blood lead values. Hänninen et al. (1979) similarly reported finding significantly increased neurological (both CNS and PNS) and gastrointestinal symptoms among 25 lead workers with maximum observed blood lead levels of 50-69 µg/dl and significantly increased CNS symptoms among 20 lower exposure workers with maximum blood lead values below 50 µg/dl, compared in each case against a referent control group (N = 23) with blood lead values of 11.9 ± 4.3 µg/dl (mean ± standard deviation).

Additional studies provide evidence of overt signs or symptoms of neurotoxicity occurring at still lower lead exposure levels than those indicated above. Baker et al. (1979) studied dose-response relationships between clinical signs and symptoms of lead intoxication among lead workers in two smelters. No toxicity was observed at blood lead levels below 40 µg/dl. However, 13 percent of those workers with blood lead values in the range 40-79 µg/dl had extensor muscle weakness or gastrointestinal symptoms; and anemia occurred in 5 percent of the workers with 40-59 µg/dl blood lead levels, in 14 percent with levels of 60-79 µg/dl, and in 36 percent with blood lead levels exceeding 80 µg/dl. Also, Fischbein et al. (1980), in a study of 90 cable splicers intermittently exposed to lead, found higher zinc protoporphyrin levels (an indicator of impaired heme synthesis associated with lead exposure) among workers reporting CNS or gastrointestinal symptoms than among other cable splicers not reporting such symptoms. Only 5 percent of these workers had blood lead levels in excess of 40 µg/dl, and the mean ± standard deviation blood lead levels for the 26 reporting CNS symptoms were 28.4 ±7.6 µg/dl and 30 ±9.4 µg/dl for the 19 reporting gastrointestinal symptoms. Caution must be exercised in accepting these blood levels as being representative of average or maximum lead exposures of this worker population, however, in view of the highly intermittent nature of their exposure and probable much higher resulting peaks in their blood lead levels than those coincidentally measured at the time of their blood sampling.

Overall, the above results appear to support the following conclusions: (1) overt signs and symptoms of neurotoxicity in adults are manifested at roughly comparable lead exposure levels as other types of overt signs and symptoms of lead intoxication, such as gastrointestinal complaints; (2) the neurological signs and symptoms are indicative of both central and peripheral nervous system effects; (3) such overt signs and symptoms, both neurological and otherwise, occur at markedly lower blood lead levels than the 60 or 80 µg/dl criteria levels

previously established or recently discussed as being "safe" for occupationally exposed adults; and (4) lowest observed effect levels for the neurological signs and symptoms can most credibly be stated to be in the 40 to 60 µg/dl range. Insufficient information exists presently by which to estimate with confidence to what extent or for how long such overt signs and symptoms persist in adults after termination of precipitating external lead exposures, but at least one study (Dahlgren, 1978) reports evidence of abdominal pain persisting for as long as 29 months after exposure termination among 15 smelter workers, including four whose blood lead levels were between 40 and 60 µg/dl while working.

12.4.2.1.2 Non-Overt lead intoxication in adults. Of special importance for establishing standards for exposure to lead is the question of whether exposures lower than those producing overt signs or symptoms of lead intoxication result in less obvious neurotoxic effects in otherwise apparently healthy individuals. Attention has focused in particular on whether exposures leading to blood lead levels below 80-100 µg/dl may lead to behavioral deficits or other neurotoxic effects in the absence of classical signs of overt lead intoxication.

In adults, if such neurobehavioral deficits occurred with great frequency, one might expect this to be reflected by performance measures in the workplace, such as higher rates of absences or reduced psychomotor performances among occupationally exposed lead workers. Some epidemiological studies have investigated possible relationships between elevated blood lead and general health as indexed by records of sick absences certified by physicians (Araki et al., 1982; Robinson, 1976; Shannon et al., 1976; Tola and Nordman, 1977). However, sickness absence rates are generally poor epidemiologic outcome measures that may be confounded by many variables and are difficult to relate specifically to lead exposure levels. Much more useful are studies discussed below which evaluate lead exposures in relation to direct measurements of CNS or peripheral neurological functions.

Only a few studies have employed sensitive psychometric and/or neurological testing procedures in an effort to demonstrate specific lead-induced neurobehavioral effects in adults. For example, Morgan and Repko (1974) reported deficits in hand-eye coordination and reaction time in an extensive study of behavioral functions in 190 lead-exposed workers (mean blood lead level = 60.5 ± 17.0 µg/dl). The majority of the subjects were exposed between 5 and 20 years. In a similar study, Milburn et al. (1976) found no differences between control and lead-exposed workers on numerous psychometric and other performance tests. On the other hand, several recent studies (Arnvig et al., 1980; Grandjean et al., 1978; Hänninen et al., 1978; Mantere et al., 1982; Valciukas et al., 1978) have found disturbances in visual motor performance, IQ test performance, hand dexterity, mood, nervousness, and coping in lead workers with blood lead levels of 50-80 µg/dl. A graded dose-effect relationship for non-overt CNS lead effects in otherwise apparently asymptomatic adults is indicated by such studies.

In addition to the above studies indicative of CNS dysfunctions in non-overtly lead intoxicated adults, numerous investigations have provided electrophysiological data indicating that peripheral nerve dysfunction in apparently asymptomatic adults can be associated with blood lead values below 80 µg/dl. Such peripheral nerve deficits, i.e. slowed nerve conduction veolocity (NCV), were established by Seppäläinen et al. (1975) for lead workers whose blood lead levels were as low as 50 µg/dl and had never exceeded 70 µg/dl during their entire exposure period (mean = 4.6 years), as determined by regular monitoring. Similar results were obtained in a study by Melgaard et al. (1976) on automobile mechanics exposed to TEL and other lead compounds in lubricating and high-pressure oils. Results of an analysis of the workers' blood for lead, chromium, copper, nickel, and manganese indicated a clear association between lead exposure and peripheral nerve dysfunction. Half of the workers (10 to 20) had elevated blood lead levels (60-120 µg/dl) and showed definite electromyographic deficits. The mean blood lead level for the control group was 18.6 µg/dl. Melgaard et al. (1976) reported additional results on associating lead exposures with polyneuropathy of unknown etiology in 10 cases from the general population. Another study reported by Araki and Honma (1976) provided further confirmation of the Seppäläinen et al. (1975) and Melgaard et al. (1976) findings in that evidence for peripheral neuropathy effects were reported for lead industry workers with blood lead values of 29 to 70 µg/dl.

More recent studies by Araki et al (1980), Ashby (1980), Bordo et al. (1982), Johnson et al. (1980), Seppäläinen et al. (1979), and Seppäläinen and Hernberg (1980, 1982) have confirmed a dose-dependent slowing of NCV in lead workers with blood lead levels below 70 to 80 µg/dl. Seppäläinen et al. (1979) observed NCV slowing in workers with blood lead levels across a range of 29 to 70 µg/dl (Figure 12-2); and Seppäläinen and Hernberg (1980, 1982) found NCV slowing in workers with maximum blood lead levels of 30 to 48 µg/dl, but not among workers with levels below 30 µg/dl. Buchthal and Behse (1979), Lilis et al. (1977), and Paulev et al. (1979), in contrast, found no signs of neuropathy below 80 µg/dl. Reports of low blood lead levels (below 50 µg/dl) in some of the above studies should be viewed with caution until further confirmatory data are reported for larger samples using well verified blood assay results. Nonetheless, these studies are consistent with a continuous dose-response relationship between blood lead concentration and extent and degree of peripheral nerve dysfunction in non-overtly lead intoxicated adults.

The above studies on nerve conduction velocity provide convergent evidence for peripheral nerve dysfunctions occurring in adults with blood lead levels in the 30-70 µg/dl range but not exhibiting overt signs of lead intoxication. Furthermore, although it might be argued that peak levels of lead may have been significant and that substantially higher lead body burdens existing before the time of some of the studies were actually responsible for producing the dysfunctions, it appears that in several cases (Seppäläinen et al., 1975; Seppäläinen and

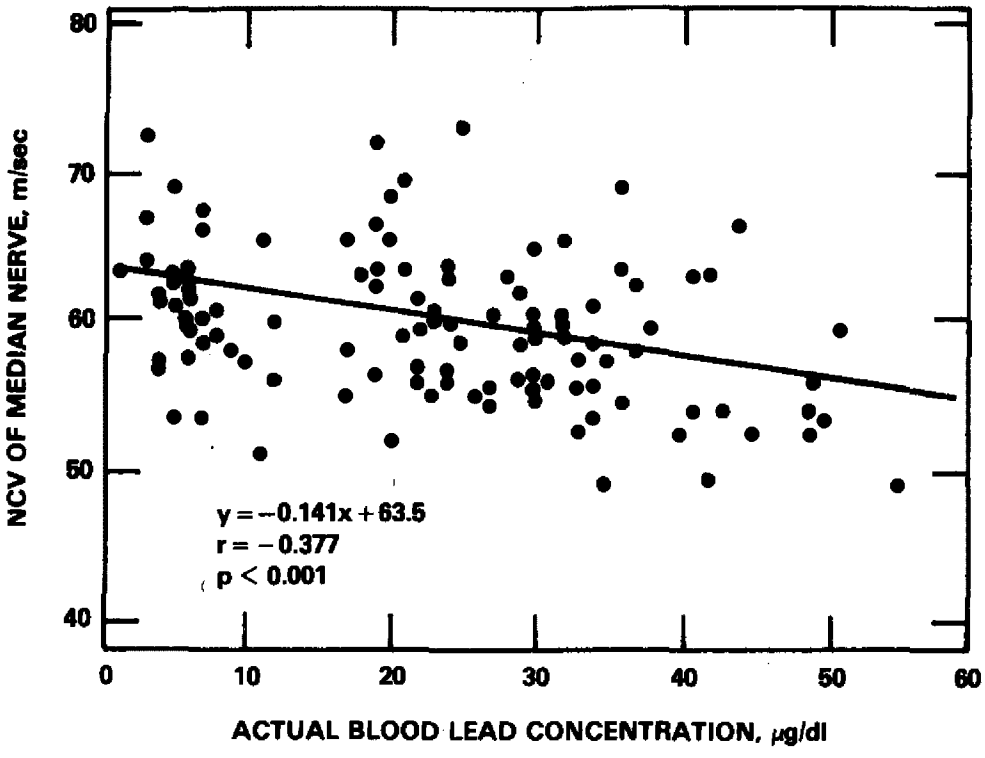

Figure 12-2. Maximal motor nerve conduction velocity (NCV) of the median nerve plotted against the actual blood lead level for 78 workers occupationally exposed to lead and for 34 control subjects.

Source: Seppäläinen et al. (1979).

Hernberg, 1980) blood levels that had never exceeded 70 µg/dl were related to increased peripheral nerve dysfunction; and, in the Seppäläinen and Hernberg (1982) study, NCV slowing was associated with maximum levels of 30-48 µg/dl. The studies by Seppäläinen and her co-workers are generally methodologically sound, having been well controlled for the possible effects of extraneous factors such as history, length, and type of exposure, multiple assessments of different nerves, temperature differences at the NCV assessment sites, plus relevant confounding covariates. Thus, when the Seppäläinen et al. (1975) results are viewed collectively with the data from other studies reviewed here, substantial evidence can be stated to exist for peripheral nerve dysfunctions occurring in adults at blood lead levels of as low as 30 to 50 µg/dl. The question as to whether these reflect mild, reversible effects (Buchthal and Behse, 1981) or are true early warning signals of progressively more serious peripheral neuropathies important in the diagnosis of otherwise unrecognized toxic effects of lead (Feldman et al., 1977; Seppäläinen and Hernberg, 1980) is still a matter of some dispute. Nevertheless, it is clear that these effects represent departures from normal neurologic functioning and their potential relationship to other extremely serious effects (see, for example, the next paragraph) argues for prudence in interpreting their potential health significance.

There are several reports of previous overexposure to heavy metals in amyotrophic lateral sclerosis (ALS) patients and patients dying of motor neuron disease (MND). Conradi et al. (1976, 1978a,b, 1980) found elevated cerebrospinal fluid lead levels in ALS patients as compared with controls. Thus, the possible pathogenic significance of lead in ALS needs to be further explored. In addition, Kurlander and Patten (1978) found that lead levels in spinal cord anterior horn cells of MND patients were nearly three times that of control subjects and that lead levels correlated with illness durations. Despite chelation therapy for about a year, high lead levels remained in their tissue.

12.4.2.2 Neurotoxic Effects of Lead Exposure in Children.

12.4.2.2.1 Overt lead intoxication in children. Symptoms of encephalopathy similar to those that occur in adults have been reported to occur in infants and young children (Prendergast, 1910; Oliver and Vogt, 1911; Blackfan, 1917; McKahann and Vogt, 1926; Giannattasio et al., 1952; Cumings, 1959; Tepper, 1963; Chisolm, 1968), with a markedly higher incidence of severe encephalopathic symptoms and deaths occurring among them than in adults. This may reflect the greater difficulty in recognizing early symptoms in young children, thereby allowing intoxication to proceed to a more severe level before treatment is initiated (Lin-Fu, 1973). In regard to the risk of death in children, the mortality rate for encephalopathy cases was approximately 65 percent prior to the introduction of chelation therapy as standard medical practice (Greengard et al., 1965; National Academy of Sciences, 1972; Niklowitz, 1975; Niklowitz and Mandybur, 1975). The following mortality rates have been reported for children

experiencing lead encephalopathy since the inception of chelation therapy as the standard treatment approach: 39 percent (Ennis and Harrison, 1950); 20 to 30 percent (Agerty, 1952); 24 percent (Mellins and Jenkins, 1955); 18 percent (Tanis, 1955); and 5 percent (Lewis et al., 1955). These data, and those tabulated more recently (National Academy of Sciences, 1972), indicate that once lead poisoning has progressed to the point of encephalopathy, a life-threatening situation clearly exists and, even with medical intervention, is apt to result in a fatal outcome. Historically there have been three stages of chelation therapy. Between 1946 and 1950, dimercaprol (BAL) was used. From 1950 to 1960, calcium disodium ethylenediaminetetraacetate (CaEDTA) completely replaced BAL. Beginning in 1960, combined therapy with BAL and CaEDTA (Chisolm, 1968) resulted in a very substantial reduction in mortality.

Determining precise values for lead exposures necessary to produce acute symptoms, such as lethargy, vomiting, irritability, loss of appetite, dizziness, etc., or later neurotoxic sequelae in humans is difficult in view of the usual sparsity of data on environmental lead exposure levels, period(s) of exposure, or body burdens of lead existing prior to manifestation of symptoms. Nevertheless, enough information is available to permit reasonable estimates to be made regarding the range of blood lead levels associated with acute encephalopathic symptoms or death. Available data indicate that lower blood lead levels among children than among adults are associated with acute encephalopathy symptoms. The most extensive compilation of information on a pediatric population is a summarization (National Academy of Sciences, 1972) of data from Chisolm (1962, 1965) and Chisolm and Harrison (1956). This data compilation relates occurrence of acute encephalopathy and death in children in Baltimore to blood lead levels determined by the Baltimore City Health Department (using the dithizone method) between 1930 and 1970. Blood lead levels formerly regarded as "asymptomatic" and other signs of acute lead poisoning were also tabulated. Increased lead absorption in the absence of detected symptoms was observed at blood lead levels ranging from 60 to 300 μg/dl (mean = 105 μg/dl). Acute lead poisoning symptoms other than signs of encephalopathy were observed from approximately 60 to 450 μg/dl (mean = 178 μg/dl). Signs of encephalopathy (hyperirritability, ataxia, convulsions, stupor, and coma) were associated with blood lead levels of approximately 90 to 700 or 800 μg/dl (mean = 330 μg/dl). The distribution of blood lead levels associated with death (mean = 327 μg/dl) was essentially the same as for levels yielding encephalopathy. These data suggest that blood lead levels capable of producing death in children are essentially identical to those associated with acute encephalopathy and that such effects are usually manifested in children starting at blood lead levels of approximately 100 μg/dl. Certain other evidence from scattered medical reports (Gant, 1938; Smith et al., 1938; Bradley et al., 1956; Bradley and Baumgartner, 1958; Cumings, 1959; Rummo et al., 1979), however, suggests that acute encephalopathy in the most highly susceptible children may be associated with blood lead levels in the range of 80-100 μg/dl. These latter reports are evaluated in detail in the 1977 EPA document Air Quality Criteria for Lead (U.S. EPA, 1977).

From the preceding discussion, it can be seen that severity of symptoms varies widely for different adults or children as a function of increasing blood lead levels. Some show irreversible CNS damage or death at blood lead levels around 100 µg/dl, whereas others may not show any of the usual clinical signs of lead intoxication even at blood lead levels in the 100 to 200 µg/dl or higher range. This diversity of response may be due to: (1) individual biological variation in lead uptake or susceptibility to lead effects; (2) changes in blood lead values from the time of initial damaging intoxication; (3) greater tolerance for a gradually accumulating lead burden; (4) other interacting or confounding factors, such as nutritional state or inaccurate determinations of blood lead; or (5) lack of use of blind evaluation procedures on the part of the evaluators. It should also be noted that a continuous gradation of frequency and severity of neurotoxic symptoms extends into the lower ranges of lead exposure.

Morphological findings vary in cases of fatal lead encephalopathy among children (Blackman, 1937; Pentschew, 1965; Popoff et al., 1963). Reported neuropathologic findings are essentially the same for adults and children. On macroscopic examination the brains are often edematous and congested. Microscopically, cerebral edema, altered capillaries (endothelial hypertrophy and hyperplasia), and perivascular glial proliferation often occur. Neuronal damage is variable and may be caused by anoxia. However, in some cases gross and microscopic changes are minimal (Pentschew, 1965). Pentschew (1965) described neuropathology findings for 20 cases of acute lead encephalopathy in infants and young children. The most common finding was activation of intracerebral capillaries characterized by dilation of the capillaries, with swelling of endothelial cells. Diffuse astrocytic proliferation, an early morphological response to increased permeability of the blood-brain barrier, was often present. Concurrent with such alterations, especially evident in the cerebellum, were changes that Pentschew (1965) attributed to hemodynamic disorders, i.e., ischemic changes manifested as cell necrosis, perineuronal incrustations, and loss of neurons, especially in isocortex and basal ganglia.

Attempts have been made to understand better brain changes associated with encephalopathy by studying animal models. Studies of lead intoxication in the CNS of developing rats have shown vasculopathic changes (Pentschew and Garro, 1966), reduced cerebral cortical thickness and reduced number of synapses per neuron (Krigman et al., 1974a), and reduced cerebral axonal size (Krigman et al., 1974b). Biochemical changes in the CNS of lead-treated neonatal rats have also demonstrated reduced lipid brain content but no alterations of neural lipid composition (Krigman et al., 1974a) and a reduced cerebellar DNA content (Michaelson, 1973). In cases of lower level lead exposure, subjectively recognizable neuropathologic features may not occur (Krigman, 1978). Instead there may be subtle changes at the level of the synapse (Silbergeld et al., 1980a) or dendritic field, myelin-axon relations, and organization of

synaptic patterns (Krigman, 1978). Since the nervous system is a dynamic structure rather than a static one, it undergoes compensatory changes (Norton and Culver, 1977), maturation and aging (Sotelo and Palay, 1971), and structural changes in response to environmental stimuli (Coss and Glohus, 1978). Thus, whereas massive structural damage in many cases of acute encephalopathy would be expected to lead to lasting neurotoxic sequalae, some other CNS effects due to severe early lead insult might be reversible or compensated for, depending upon age and duration of toxic exposure. This raises the question of whether effects of early overt lead intoxication are reversible beyond the initial intoxication or continue to persist.

In cases of severe or prolonged nonfatal episodes of lead encephalopathy, there occur neurological sequelae qualitatively similar to those often seen following traumatic or infectious cerebral injury, with permanent sequelae being more common in children than in adults (Mellins and Jenkins, 1955; Chisolm, 1962, 1968). The most severe sequelae in children are cortical atrophy, hydrocephalus, convulsive seizures, and severe mental retardation (Mellins and Jenkins, 1955; Perlstein and Attala, 1966; Chisolm, 1968). Children who recover from acute lead encephalopathy but are re-exposed to lead almost invariably show evidence of permanent central nervous system damage (Chisolm and Harrison, 1956). Even if further lead exposure is minimized, 25 to 50 percent show severe permanent sequelae, such as seizure disorders, blindness, and hemiparesis (Chisolm and Barltrop, 1979).

Lasting neurotoxic sequelae of overt lead intoxication in children in the absence of acute encephalopathy have also been reported. Byers and Lord (1943), for example, reported that 19 out of 20 children with previous lead poisoning later made unsatisfactory progress in school, presumably due to sensorimotor deficits, short attention span, and behavioral disorders. These latter types of effects have since been confirmed in children with known high exposures to lead, but without a history of life-threatening forms of acute encephalopathy (Chisolm and Harrison, 1956; Cohen and Ahrens, 1959; Kline, 1960). Perlstein and Attala (1966) also reported neurological sequelae in 140 of 386 children (37 percent) following lead poisoning without encephalopathy. Such sequelae included mental retardation, seizures, cerebral palsy, optic atrophy, and visual-perceptual problems in some children with minimal intellectual impairment. The severity of sequelae was related to severity of earlier observed symptoms. For 9 percent of those children who appeared to be without severe symptoms at the time of diagnosis of overt lead poisoning, mental retardation was observed upon later follow-up. The conclusion of the neurological effects observed by Perlstein and Attala (1966) being persisting effects of earlier overt lead intoxication without encephalopathy might be questioned in view of no control group having been included in the study; however, it is extremely unlikely that 37 percent of any randomly selected control group from the general pediatric population would exhibit the types of neurological problems observed in that proportion of the cohort of children with earlier lead intoxication studied by Perlstein and Attala (1966).

Numerous studies (Cohen et al., 1976; Fejerman et al., 1973; Pueschel et al., 1972; Sachs et al., 1978, 1979, 1982) suggest that, in the absence of encephalopathy, chelation therapy may ameliorate the persistence of neurotoxic effects of overt lead poisoning (especially cognitive, perceptual, and behavioral deficits). On the other hand, one recent study found a residual effect on fine motor performance even after chelation (Kirkconnell and Hicks, 1980).

In summary, pertinent literature definitively demonstrates that lead poisoning with encephalopathy results in a greatly increased incidence of permanent neurological and cognitive impairments. Also, several studies further indicate that children with symptomatic lead poisoning in the absence of encephalopathy also show a later increased incidence of neurological and behavioral impairments.

12.4.2.2.2 Non-Overt lead intoxication in children

In addition to neurotoxic effects associated with overt lead intoxication in children, growing evidence indicates that lead exposures not leading to overt lead intoxication in children can induce neurological dysfunctions. This issue has attracted much attention and generated considerable controversy during the past 10 to 15 years. However, the evidence for and against the occurrence of significant neurotoxic deficits at relatively low levels of lead exposure is quite mixed and largely interpretable only after a thorough critical evaluation of methods employed in the various important studies on the subject. Based on the five criteria listed earlier (i.e., adequate markers of exposure to lead, sensitive measures, appropriate subject selection, control of confounding covariates, and appropriate statistical analysis), the 20 population studies summarized in Table 12-1 were conducted rigorously enough to warrant at least some consideration here. Even so, no epidemiological study is completely flawless and, therefore, overall interpretation of such findings must be based on evaluation of: (1) the internal consistency and quality of each study; (2) the consistency of results obtained across independently conducted studies; and (3) the plausibility of results in view of other available information.

Rutter (1980) has classified studies evaluating neurobehavioral effects of lead exposure in non-overtly lead intoxicated children according to several types, including four categories reviewed below: (1) clinic-type studies of children thought to be at risk because of high lead levels; (2) other studies of children drawn from general (typically urban or suburban) pediatric populations; (3) samples of children living more specifically in close proximity to lead emitting smelters; and (4) studies of mentally retarded or behaviorally deviant children. Major attention is accorded here to studies falling under the first three categories. As will be seen, quite mixed results have emerged from the studies reviewed.

12.4.2.2.2.1 Clinic-type studies of children with high lead levels. The clinic-type studies are typified by evaluation of children with relatively high lead body burdens as identified through lead screening programs or other large-scale programs focussing on mother-infant health relationships and early childhood development.

TABLE 12-1. SUMMARY OF PUBLISHED RESULTS FROM STUDIES OF LEAD EFFECTS ON NEUROBEHAVIORAL FUNCTIONS OF NON-OVERTLY LEAD INTOXICATED CHILDREN

Reference	Population studied	N/group	Age at testing, yr	Blood lead, µg/dl	Psychometric tests employed	Summary of results (C=control; Pb=lead)[a]	Levels of significance[b]
Clinic-type Studies of Children with High Lead Levels							
De la Burde and Choate (1972)	Inner city (Richmond, VA)	Control = 72 Lead = 70	4 4	Not assayed[c] 40-100[d]	Stanford-Binet IQ Other measures	C = 94 Pb = 89 C > Pb on 3/4 tests	p <0.05 N.S.-p <0.01
De la Burde and Choate (1975)	Follow-up same subjects	Control = 67 Lead = 70	7 7	See above[e] See above[e]	WISC Full Scale IQ Neurologic exam Other measures	C = 90 Pb = 87 C better than Pb C > Pb on 9/10 tests	p <0.01 p <0.01 N.S.-p <0.001
Rummo et al. (1974, 1979)	Inner city (Providence, RI)	Control Ss = 45	4-8 ($\bar{x}$ = 5.8)	$\bar{x}$ = 23 ± 8	McCarthy General Cognitive	C = 93; S = 94; L = 88; P = 77	N.S.-p <0.01 (P vs C)
		Short Pb Ss = 15	4-8 ($\bar{x}$ = 5.6)	$\bar{x}$ = 61 ± 7	McCarthy Subscales	C+S > L > P on 5/5 tests	N.S.-p <0.01 (P vs C)
		Long Pb Ss = 20	4-8 ($\bar{x}$ = 5.6)	$\bar{x}$ = 68 ± 13	Neurologic exam rating	C+S > L > P on ratings	N.S.
		Post enceph Pb = 10	4-8 ($\bar{x}$ = 5.3)	$\bar{x}$ = 88 ± 40	Objective neurologic tests	C+S > L > P on 3/12 tests	N.S.-p <0.01 (P vs C)
Kotok (1972)	Inner city (New Haven, CT)	Control = 25 Lead = 24	1.1 -5 .5 ($\bar{x}$ = 2.7) 1.0 - 5.8 ($\bar{x}$ = 2.8)	20-55 58-137	Denver Developmental Scale	C > Pb on 1/3 Subscales	N.S.
Kotok et al. (1977)	Inner city (Rochester, NY)	Control = 36 Lead = 31	1.9 - 5.6 ($\bar{x}$ = 3.6) 1.7 - 5.4 ($\bar{x}$ = 3.6)	11-40 61-200	IQ Equivalent for six ability classes: Social maturity; Spatial relations; Spoken vocab; Info. comprehension; Visual attention; Auditory memory	IQ Equivalent for each: C = 126 Pb = 124 C = 101 Pb = 92; C = 93 Pb = 92; C = 96 Pb = 95; C = 93 Pb = 90 C = 100 Pb = 93	p <0.10 for spatial p >0.10 for all other ability classes
Perino and Ernhart (1974)	Inner city (New York, NY)	Control = 50	3-6	10-30	McCarthy General Cognitive	C = 90 Pb = 80	p <0.01
		Lead = 30	3-6	40-70	McCarthy Subscales	C > Pb on 5/5 scales	N.S.-p <0.01
Ernhart et al. (1981)	Follow-up same subjects	Control = 31 Lead = 32	8-13	21.3±3.7[f] 32.4±5.3	McCarthy General Cognitive Index	Shared Variance = 7.7	p <0.05
					McCarthy Subscales Reading Tests Exploratory Tests (Bender Gestalt, Draw-A-Child)	(2/5) 8.0, 7.4 1.3 ?	p <0.05 N.S. N.S.
					Conners Teachers Rating Scale	?	N.S.

TABLE 12-1. (continued)

Reference	Population studied	N/group	Age at testing, yr	Blood lead, µg/dl	Psychometric tests employed	Summary of results (C=control; Pb=lead)[a]	Levels of significance[b]
General Population Studies							
Needleman et al. (1979)	General population (Boston, MA area)	Control = 100	7	PbT < 10 ppm[h]	WISC Full scale IQ	C = 106.6 Pb = 102.1	p < 0.03
		Lead = 58	7	PbT > 20 ppm	WISC Verbal IQ	C = 103.9 Pb = 99.3	p <0.03
					WISC Performance IQ	C = 108.7 Pb = 104.9	N.S.
					Seashore Rhythm Test	C = 21.6 Pb = 19.4	p <0.002
					Token Test	C = 24.8 Pb = 23.6	N.S.
					Sentence Repetition Test	C = 12.6 Pb = 11.3	p <0.04
					Delayed Reaction Time	C > Pb on 3/4 blocks	p <0.01
					Teacher's Behavior Rating	C = 9.5 Pb = 8.2	p <0.02
McBride et al. (1982)	Urban and suburban (Sydney, Australia)	Moderate = C.100	4,5	19-30 µg/dl	Peabody Picture Voc. Test	C = 105 Pb = 104	N.S.
		Low = C.100	4,5	0.5-9 µg/dl	Fine Motor Tracking	C > Pb 1/4 comparisons	p <0.05
					Pegboard	C = 20 Pb = 20	N.S.
					Tapping Test	C = 30 Pb = 31	N.S.
					Beam Walk	C = 5 Pb = 4	N.S.
					Standing Balance	C > Pb 1/4 comparisons	p <0.05
					Rutter Activity Scale	C = 1.9 Pb - 2.1	N.S.
Yule et al. (1981)	Urban (London, England)	Group 1 = 20	9	8.8[j]	WISC-R Full Scale IQ	Gp1 < Gp2 > Gp3 > Gp4	p <0.029
		Group 2 = 29	9	11.6	Verbal IQ	Gp1 < Gp2 > Gp3 > Gp4	p <0.04
		Group 3 = 29	8	14.5	Performance IQ	Gp1 < Gp2 > Gp3 > Gp4	N.S.
		Group 4 = 21	8	19.6	Vernon Spelling Test[k]	Gp1 > Gp2 > Gp3 > Gp4	p <0.001
					Vernon Arithmetic Test[k]	Gp1 < Gp2 > Gp3 > Gp4	N.S.
					Neale Reading Test[k]	Gp1 < Gp2 > Gp3 > Gp4	p <0.001
Yule et al. (1983)	Same subjects	Same	Same	Same	Needleman Teacher's Behavior Ratings	Linear Trend 3/4 items	p <0.05
					Conners Teachers Questionnaire Factors 1,2,4,5	Gp1 < Gps2-4	p <0.05
					Rutter Teacher Rating Scale for Activity	Linear Trend 25/36 items	N.S.

Table 12-1. (continued)

Reference	Population studied	N/group	Age at testing, yr	Blood lead, µg/dl	Psychometric tests employed	Summary of results (C=control; Pb=lead)[a]			Levels of significance[b]
						HIGH	MED	LOW	
Smith et al. (1983)	Urban (London, UK)	Hi = 155	6,7	PbT ≥ 8.0	WISC-R Full Scale	105	105	107	N.S.
		Med = 103	6,7	PbT = 5-5.5	Verbal IQ	103	103	105	N.S.
		Low = 145	6,7	PbT < 2.5	Performance IQ	106	106	108	N.S.
				(All in µg/g)					
				$\bar{x}$ PbB = 13.1 µg/dl	Word Reading Test	40	42	45	N.S.
					Seashore Rhythm Test	20	20	21	N.S.
					Visual Sequential Memory	20	19	20	N.S.
					Sentence Memory	9	9	9	N.S.
					Shape Copying	14	14	14	N.S.
					Mathematics	15	15	16	N.S.
					Mean Visual RT (secs)	.39	.37	.37	N.S.
					Conners Teachers Ratings	13	11	11	N.S.
						Low		Hi	
Yule and Lansdown (1983)	Urban (London, UK)	80	9	7-12	WISC-R Full Scale	107		105	N.S.
		82	9	13-24	Verbal IQ	104		103	N.S.
					Performance IQ	108		106	N.S.
					Neale Reading Acc.	114		111	N.S.
					Neale Reading Comp.	113		109	N.S.
					Vernon Spelling	101		99	N.S.
					Vernon Math	100		99	N.S.
Harvey et al. (1983)	Urban (Birmingham, UK)	189	2.5	15.5	British Ability Scales	Regression F Ratio			N.S.
					Naming	<1			N.S.
					Recall	1.26			N.S.
					Comprehension	<1			N.S.
					Recognition	<1			N.S.
					IQ	<1			N.S.
					Stanford-Binet Items				
					Shapes	<1			N.S.
					Blocks	2.34			N.S.
					Beads	2.46			N.S.
					Playroom Activity	?			N.S.

Table 12-1. (continued)

Reference	Population studied	N/group	Age at testing, yr	Blood lead, µg/dl	Psychometric tests employed	Summary of results (C=control; Pb=lead)[a]	Levels of significance[b]
Smelter Area Studies							
Landrigan et al. (1975)	Smelter area (El Paso, TX)	Control = 46 Lead = 78	3-15 ($\bar{x}$ = 9.3) 3-15 (x = 8.3)	<40 40-68	WISC Full Scale IQ[f] WPPSI Full Scale IQ[g] WISC + WPPSI Combined WISC + WPPSI Subscales Neurologic testing	C = 93 Pb = 87 C = 91 Pb = 86 C = 93 Pb = 88 C > Pb on 13/14 scales C > Pb on 4/4 tests	N.S. N.S. p <0.01 N.S.-p <0.01 N.S.-p <0.001
McNeil and Ptasnik (1975)	Smelter area (El Paso, TX)	Control = 61-152 Lead = 23-161	1.5 - 18(Mdn = 9) 1.5 - 18(Mdn = 9)	<40 >40	McCarthy General Cognitive WISC-WAIS Full Scale IQ Oseretsky Motor Level California Personality Frostig Perceptual Quotient Finger-Thumb Apposition	C = 82 Pb = 81 C = 89 Pb = 87 C = 101 Pb = 97 C > Pb, 6/10 items C = 100 Pb = 103 C = 27 Pb = 29	N.S. N.S. N.S. p <0.05 N.S. N.S.
Ratcliffe (1977)	Smelter area Manchester, Eng.	Control = 23 Lead = 24	4-7 4-8	28.2 44.4	Griffiths Mental Dev. Frostig Visual Perception Pegboard Test	C = 101-111 Pb = 97-107 C = 14.3 Pb = 11.8 C = 17.5 Pb = 17.3 C = 19.5 Pb = 19.8	N.S. N.S. N.S. N.S.
Winneke et al. (1982a)	Smelter area (Duisburg, FRG)	Control = 26 Lead = 26	8 8	PbT = 2.4 ppm[h] PbT = 9.2 ppm No PbB	German WISC Full Scale Verbal IQ Performance IQ Bender Gestalt Test Standard Neurological Tests Conners Teachers Rating Scale	C = 122 Pb = 117 C = 130 Pb = 124 C = 130 Pb = 123 C = 17.2 Pb = 19.6 C = 2.7 Pb = 7.2 C = ? Pb = ?	N.S. N.S. N.S. p <0.05 N.S. N.S.
Winneke et al. (1982b)	Smelter area (Stolburg, FRG)	89	9.4	PbT = 6.16 ppm[h] PbB = 14.3 µg/dl	German WISC Full Scale IQ Verbal IQ Performance IQ Bender Gestalt Test Standard Neurological Tests Conners Teachers Rating Scale Wiener Reaction Performance	Prop. of Variance=-0.0 -0.5 +0.6 +2.1 +1.2 0.4-1.3 +2.0	N.S. N.S. N.S. p <0.05 N.S. N.S. N.S.

[a]Mean test scores for control children indicated by C = $\bar{x}$; mean scores for respective lead-exposed groups indicated by Pb = $\bar{x}$, except for Rummo (1979) study where C = control, S = short-term lead-exposed subjects, L = long-term lead-exposed group, and P = post-encephalopathy lead group. [b]N.S. = non-significant, i.e. p >0.05. Note exception of p <0.10 listed for spacial ability results in Kotok et al. (1977) study. Significance levels are those found after partialing out confounding covariates. [c]Urinary coproporphyrin levels were not elevated. [d]Or ≥30 µg/dl with positive radiologic findings, suggesting earlier exposure in excess of 50-60 µg/dl. [e]Assays for lead in teeth showed the Pb-exposed group to be approximately twice as high as controls (202 µg/g vs. 112 µg/g, respectively). [f]Used for children over 5 years of age. [g]Used for children under 5 years of age. [h]Main measure was dentine lead (PbT). [i]Dentine levels not reported for statistical reasons. [j]Blood lead levels taken 9-12 months prior to testing; none above 33 µg/dl. [k]Data not corrected for age.

Of the several pediatric studies presenting evidence for CNS deficits being associated with lead exposure in asymptomatic children, most all are either retrospective or cross-sectional studies except the work of De la Burde and Choate (1972, 1975). De la Burde and Choate (1972) observed neurological dysfunctions, fine motor dysfunction, impaired concept formation, and altered behavioral profiles in 70 preschool children exhibiting pica and elevated blood lead levels (in all cases above 30 μg/dl; mean = 59 μg/dl) in comparison with matched control subjects not engaging in pica. Subjects were drawn from the Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurologic Disorders of Infancy and Childhood (Broman et al., 1975), which was conducted in Richmond, Virginia, and had a total population of 3400 mothers. The De la Burde and Choate study population was drawn from this group, in which all mothers were followed throughout pregnancy and all children were postnatally evaluated by regular pediatric neurologic examinations, psychological testing, and medical interviews. All children subject to prenatal, perinatal, and early postnatal insults were excluded from the study, and all had to have normal neurologic examinations and Bayley tests at eight to nine months of age. These are important points which add value to the study. It is unfortunate that blood lead data were not regularly obtained; however, at the time of the study in the late 1960s, 10 to 20 ml of venous blood was required for a blood lead determination and such samples usually had to be obtained by either jugular or femoral puncture. The other control features (housing location and repeated urinary coproporphyrin tests) would be considered the state of the art for such a study at the time that it was carried out.

In a follow-up study on the same children (at 7 to 8 years old), De la Burde and Choate (1975) reported continuing CNS impairment in the lead-exposed group as assessed by a variety of psychological and neurological tests. In addition, seven times as many lead-exposed children were repeating grades in school or being referred to the school psychologist, despite many of their blood lead levels having by then dropped significantly from the initial study. In general, the De la Burde and Choate (1972, 1975) studies appear to be methodologically sound, having many features that strengthen the case for the validity of their findings. For example, there were appreciable numbers of children (67 lead-exposed and 70 controls) whose blood lead values were obtained in preschool years and who were old enough (7 years) during the follow-up study to cooperate adequately for reliable psychological testing. The psychometric tests employed were well standardized and acceptable as sensitive indicators of neurobehavioral dysfunction, and the testing was carried out in a blind fashion (i.e., without the evaluators knowing which were control or lead-exposed subjects).

The De la Burde and Choate (1972, 1975) studies might be criticized on several points, but none provide sufficient grounds for rejecting their results. One difficulty is that blood lead values were not determined for control subjects in the initial study; but the lack of history of pica, as well as tooth lead analyses done later for the follow-up study, render it improbable that appreciable numbers of lead-exposed subjects might have been wrongly assigned to the control group. Subjects in the control group did have a history of pica, but not for paint. Also, results indicating no measurable coproporphyrins in the urine of control subjects at the time of initial testing further confirm proper assignment of those children to the nonexposed control group. A second point of criticism is the use of multiple chi-square statistical analyses, but the fact that the control subjects did significantly better on virtually every measure makes it unlikely that all of the observed effects were due to chance alone. One last problem concerns ambiguities in subject selection which complicate interpretation of the results obtained. Because the lead-exposed group included children with blood lead levels of 40 to 100 μg/dl, or of at least 30 μg/dl with "positive radiographic findings of lead lines in the long bones, metallic deposits in the intestines, or both," observed deficits might be attributed to blood lead levels as low as 30 μg/dl. Other evidence (Betts et al., 1973), however, suggests that such a simple interpretation is probably not accurate. That is, the Betts et al. (1973) study indicates that lead lines are usually seen only if blood levels exceed 60 μg/dl for most children at some time during exposure, although some (about 25 percent) may show lead lines at blood lead levels of 40 to 60 μg/dl. In view of this, the de la Burde and Choate results can probably be most reasonably interpreted as showing persisting neurobehavioral deficits at blood lead levels of 40 to 60 μg/dl or higher.

In another clinic-type child study, Rummo et al. (1974, 1979), found significant neurobehavioral deficits (hyperactivity, lower scores on McCarthy scales of cognitive function, etc.) among Providence, Rhode Island, inner-city children who had previously experienced high levels of lead exposure that had produced acute lead encephalopathy. Mean maximum blood lead levels recorded for those children at the time of encephalopathy were 88 ± 40 μg/dl. However, children with moderate blood lead elevation but not manifesting symptoms of encephalopathy were not significantly different (at $p < 0.05$) from controls on any measure of cognitive functioning, psychomotor performance, or hyperactivity. Still, when the data from the Rummo et al. (1979) study for performance on the McCarthy General Cognitive Index or several McCarthy Subscales are compared (see Table 12-1), the scores for long-term moderate-exposure subjects consistently fall below those for control subjects and lie between the latter and the encephalopathy group scores. Thus, it appears that long-term moderate lead exposure may have, in fact, exerted dose-related neurobehavioral effects. The overall dose-response trend might have been shown to be statistically significant if other types of analyses were used or if

larger samples were assessed. However, control for confounding variables in the different exposure groups would also have to be considered. Note that (1) the maximum blood lead levels for the short-term and long-term exposure subjects were all greater than 40 μg/dl (means = 61 ± 7 and 68 ± 13 μg/dl, respectively), whereas control subjects all had blood lead levels below 40 μg/dl (mean = 23 ± 8 μg/dl), and (2) the control and lead-exposed subjects were inner-city children well matched for socioeconomic background, parental education levels, incidence of pica, and other pertinent factors, but not parental IQ.

A somewhat similar pattern of results emerged from a study by Kotok et al. (1977) in which 36 Rochester, New York, control-group children with blood lead levels less than 40 μg/dl were compared with 31 children having distinctly elevated blood lead levels (61 to 200 μg/dl) but no classical lead intoxication symptoms. Both groups were well matched on important background factors, notably including their propensity to exhibit pica. Again, no clearly statistically significant differences between the two groups were found on numerous tests of cognitive and sensory functions. However, mean scores of control-group children were consistently higher than those of the lead-exposed group for all six of the ability classes listed. Kotok (1972) had reported earlier that developmental deficiencies (using the comparatively insensitive Denver Development Screening test) in a group of children having elevated lead levels (58 to 137 μg/dl) were identical to those in a control group similar in age, sex, race, environment, neonatal condition, and presence of pica, but whose blood lead levels were lower (20 to 55 μg/dl). Children in the lead-exposed group, however, had blood lead levels as high as 137 μg/dl, whereas some control children had blood lead levels as high as 55 μg/dl. Thus, the study essentially compared two groups with different degrees of markedly elevated lead exposure rather than one of lead-exposed vs. nonexposed control children.

Perino and Ernhart (1974) reported a relationship between neurobehavioral deficits and blood lead levels ranging from 40 to 70 μg/dl in a group of 80 inner-city preschool black children, based on the results of a cross-sectional study including children detected as having elevated lead levels via the New York City lead screening program. One key result reported was that the high-lead children had McCarthy Scale IQ scores markedly lowe than those of the low-lead group (mean IQ = 90 vs 80, respectively). Also, the normal correlation of 0.52 between parents' intelligence and that of their offspring was found to be reduced to only 0.10 in the lead-exposed group, presumably because of the influence of another factor (lead) that interfered with the normal intellectual development of the lead-exposed children. One obvious possible alternative explanation for the reported results, however, might be differences in the educational backgrounds of parents of the control subjects when compared with lead-exposed subjects, because parental education level was found to be significantly negatively related to blood lead levels of the children participating in the Perino and Ernhart

(1974) study. The importance of this point lies in the fact that several other studies (McCall et al., 1972; Elardo et al., 1975; Ivanans, 1975) have demonstrated that higher parental education levels are associated with more rapid development and higher intelligence quotients (IQs) for their children.

Ernhart et al. (1981) were able to follow up 63 of the 80 preschool children of the Perino and Ernhart (1974) study once they reached school age, using the McCarthy IQ scales, various reading achievement tests, the Bender-Gestalt test, the Draw-A-Child test, and the Conners Teacher's Questionnaire for hyperactivity. The children's blood lead levels correlated significantly with FEP ($r = 0.51$) and dentine lead levels ($r = 0.43$), but mean blood lead levels of the moderately elevated group had decreased after five years. When control variables of sex and parent IQ were extracted by multivariate analyses, the observed differences were reported to be greatly reduced but remained statistically significant for three of seven tests on the McCarthy scales in relation to concurrently measured blood lead levels but not in relation to the earlier blood lead levels for the same children. This led Ernhart et al. (1981) to reinterpret their 1974 (Perino and Ernhart, 1974) IQ results (in which they had not controlled for parental education) as either not likely being due to lead or, if due to lead, then representing only minimal effects on intelligence.

The Perino and Ernhart (1974) and Ernhart et al. (1981) studies were intensively reviewed by an expert committee convened by EPA in March, 1983 (see Appendix 12-C). The committee found that blood lead measurements used in the Perino and Ernhart (1974) study were of acceptable reliability and the psychometric measures for children were acceptable. However, the IQ measure used for their parents was of questionable utility, other confounding variables may not have been adequately measured, and the statistical analyses did not deal adequately with confounding variables. As for the Ernhart et al. (1981) follow-up study, the committee found the psychometric measures to be acceptable, but the blood lead sampling method raised questions about the reliability of the reported blood lead levels and the statistical analyses did not adequately control for confounding factors. The committee concluded, therefore, that the Perino and Ernhart (1974) and Ernhart et al. (1981) study results, as published, neither confirm nor refute the hypothesis of associations between neuropsychologic deficits and low-level lead exposures in children. It was also recommended that the entire Ernhart data set be reanalyzed, using statistical analyses that better control for confounding factors and including longitudinal analyses of data for subjects that were evaluated in both the Perino and Ernhart (1974) and the Ernhart et al. (1981) studies. A sample longitudinal analysis provided by one committee member, using uncorrected blood lead values and unadjusted psychometric scores from such subjects, suggested that an association may exist between changes in blood lead levels and changes in IQ scores from the first to the second sampling point.

Two recent reports of a study of 193 children from the Philadelphia cohort of the Collaborative Perinatal Project at age seven years examined the persistence of lead-related neuropsychological deficits using circumpulpal rather than primary dentine lead assays at ages 10-14 years (Shapiro and Marecek, 1983, Marecek et al., 1983). Performance differences on several subtests of the Wechsler Intelligence Scale for Children (WISC) and Bender-Gestalt Test were found to persist after four years, these effects being more evident when related to circumpulpal than to primary dentine lead levels. Methodologically, this study suffers from sampling bias, subject ascertainment bias, poor control of covarying social factors, and use of different testers at different testing periods, with no notation as to their blindess.

Odenbro et al. (1983) studied psychological development of children (aged 3-6 yr) seen in Chicago Department of Health Clinics (August, 1976 - February, 1977), evaluating Denver Development Screening test (DDST) and Wechsler IQ scales (WPPSI) scores in relation to blood lead levels obtained by repeated sampling during the three previous years. A significant correlation ($r = -0.435$, $p < 0.001$) was reported between perceptual-visual-motor ability and mean blood levels measured. Statistically significant ($p < 0.005$) deficits in verbal productivity and perceptual visual motor performance (measured by the WPPSI) were found for children with mean blood lead levels of 30-40 µg/dl versus control children with mean blood lead levels <25 µg/dl, using two-tailed Student's t-tests. These results are highly suggestive of neuropsychologic deficits being associated with blood lead levels of 30-60 µg/dl in preschool children. However, questions can be raised regarding the adequacy of the statistical analyses employed, especially in regard to sufficient control for confounding covariates, e.g., parental IQ, education, and socioeconomic status.

The above studies generally found higher lead-exposure groups to do more poorly on IQ or other types of psychometric tests. However, many studies did not control for importtant confounding variables or, when such were taken into account, differences between lead exposed and control subjects were often no longer statistically significant. Still, the consistency of finding lower IQ values among at-risk higher lead children across the studies lends credence to cognitive deficits occurring in apparently asymptomatic children with relatively high blood lead levels. The De la Burde studies in particular point to 40-60 µg/dl as likely lowest observed effect levels among such children.

12.4.2.2.2.2 General population studies. These studies evaluated samples of non-overtly lead intoxicated children drawn from and thought to be representative of the general pediatric population. They generally aimed to evaluate asymptomatic children with lower lead body burdens than those of children in most of the above clinic-type studies.

A pioneering, general population study was reported by Needleman et al. (1979), who used shed deciduous teeth to index lead exposure. Teeth were donated from 70 percent of a total population of 3329 first and second grade children from two towns near Boston. Almost all

children who donated teeth (2146) were rated by their teachers on an eleven-item classroom behavior scale devised by the authors to assess attention disorders. An apparent dose-response function was reported for ratings on the behavior scale not taking potentially confounding variables into account. After excluding various subjects for control reasons, two groups (<10th and >90th percentiles of primary dentine lead levels) were provisionally selected for further in-depth neuropsychologic testing. Later, some provisionally eligible children were also excluded for various reasons, leaving 100 low-lead (<10 ppm dentine lead) children for comparison with 58 high-lead (>20 ppm dentine lead) children in statistical analyses reported by Needleman et al. (1979). A preliminary analysis on 39 non-lead variables showed significant differences between the low- high-lead groups for age, maternal IQ and education, maternal age at time of birth, paternal SES, and paternal education. Some of these variables were entered as covariates into an analysis of covariance along with lead. Significant effects ($p < 0.05$) were reported for full-scale WISC-R IQ scores, WISC-R verbal scales scores, for 9 of 11 classroom behavior scale items, and several experimental measures of perceptual-motor behavior.

Additional papers published by Needleman and coworkers report on results of the same or further analyses of the data discussed in the initial paper by Needleman et al. (1979). For example, a paper by Needleman (1982) provided a summary overview of findings from the Needleman et al. (1979) study and findings reported by Burchfiel et al. (1980) that are discussed later in this section concerning EEG patterns for a subset of children included in the 1979 study. Needleman (1982) summarized results of an additional analysis of the 1979 data set reported elsewhere by Needleman, Levitan and Bellinger (1982). More specifically, cumulative frequency distributions of verbal IQ scores for low- and high-lead subjects from the 1979 study were reported by Needleman et al. (1982), and the key point made was that the average IQ deficit of four points demonstrated by the 1979 study did not just reflect children with already low IQs having their cognitive abilities further impaired. Rather the entire distribution of IQ scores across all IQ levels was shifted downward in the high-lead group, with none of the children in that group having verbal IQs over 125. Another paper, by Bellinger and Needleman (1983), provided still further follow-up analyses of the 1979 N. Eng. J. Med. data set, focusing mainly on comparison of the low- and high-lead children's observed versus expected IQs based on their mother's IQ. Bellinger and Needleman reported that regression analyses showed that IQs of children with elevated levels of dentine-lead (>20 ppm) fell below those expected based on their mothers' IQs and the amount by which a child's IQ falls below the expected value increases with increasing dentine-lead levels in a nonlinear fashion. Scatter plots of IQ residuals by dentine-lead levels, as illustrated and discussed by Bellinger and Needleman (1983), indicated that regressions for children with 20-29.9 ppm dentine lead in the high-lead

group did not reveal significant associations between increasing lead levels in that range and IQ residuals, in contrast to statistically significant ($p < 0.05$) correlations between IQ residuals and dentine-lead for high-lead group children with 30-39.9 ppm dentine lead levels.

The Needleman et al. (1979) study and spin-off analyses published later by Needleman and coworkers were critically evaluated by the same expert committee noted above that was convened by EPA in March, 1983, and which evaluated the Perino and Ernhart (1974) and Ernhart et al. (1981) studies (see Appendix 12-C). In regard to the original study reported by Needleman et al. (1979), the expert committee found that dentine-lead was adequately determined as a measure of cumulative lead exposure and the psychometric data for the subject children generally appeared to be adequately collected and of acceptable reliability. However, the committee concluded that the reported dose-response relationship between dentine-lead levels and teachers' ratings of classroom behavior cannot be accepted as valid, due to: (1) serious reservations regarding the adequacy of classification of subjects into lead exposure categories using only the first dentine-lead level obtained for each child and (2) failure to control for effects of confounding variables. The committee also found that the reported statistically significant effects of lead on IQ and other behavioral neuropsychologic abilities measured for the low- and high-lead groups could not be accepted as valid, due to: (1) errors made in calculations of certain parental IQ scores entered as a control variable in analyses of covariance; (2) failure to take age and father's education into account adequately in the analyses of covariance; (3) use of a forward elimination approach rather than a backwards elimination strategy in statistical analyses; (4) concerns regarding the basis for classification of children in terms of dentine-lead levels; and (5) questions about possible bias due to exclusion of data for large numbers of provisionally eligible subjects from statistical analyses. The committee concluded, therefore, that the study results, as published by Needleman et al. (1979), neither confirm nor refute the hypothesis of associations between neuropsychologic deficits and low-level lead exposure in non-overtly lead intoxicated children. In regard to the publications by Needleman (1982), Needleman et al. (1982), and Bellinger and Needleman (1983) describing further analyses of the same data set reported on by Needleman et al. (1979), the committee concluded that the findings reported in these later papers also cannot be accepted as valid, in view of the above reservations regarding the basic analyses reported by Needleman et al. (1979) and additional problems with the later "spin-off" analyses. The committee also recommended that the entire Needleman data set be reanalyzed, correcting for errors in data calculation and entry, using better Pb exposure classification, and appropriately adjusting for confounding factors.

A recent study of urban children in Sydney, Australia (McBride et al., 1982) involved 454 preschoolers (aged 4-5 yr) with blood lead levels of 2 to 29 μg/dl. Children born at the Women's Hospital in Sydney were recruited via personal letter. No blood lead measures were

available on non-participants. Blood levels were evaluated after neurobehavioral testing, but earlier exposure history was apparently not assessed. Using a multiple statistical comparison procedure and Bonferroni correction to protect against study-wise error, no statistically significant differences were found between two groups with blood lead levels more than one standard deviation above and below the mean (>19 μg/dl vs. <9 μg/dl) on the Peabody Picture Vocabulary IQ Test, on a parent rating scale of hyperactivity devised by Rutter, or on three tests of motor ability (pegboard, standing balance, and finger tapping). In one test of fine motor coordination (tracking), five-year old boys in the higher lead group performed worse than boys in the lower lead group. In one test of gross motor skill (walking balance), results for the two age groups were conflicting. This study suffers from many methodological weaknesses and cannot be regarded as providing evidence for or against an effect of low-level lead exposures in non-overtly lead intoxicated children. For example, a comparison of socioeconomic status (father's occupation and mother's education) of the study sample with the general population showed that it was higher than Bureau of Census statistics for the Australian work force as a whole. There was apparently some self-selection bias due to a high proportion of professionals living near the hospital. Also, other demographic variables such as mother's IQ, pica, and caregiving environment were not evaluated.

Another recent large scale study (Smith et al., 1983) of tooth lead, behavior, intelligence and a variety of other psychological skills was carried out in a general population sample of over 4000 children aged 6 to 7 years in three London boroughs, 2663 of whom donated shed teeth for analysis. Of these, 403 children were selected to form six groups, one each of high (8 μg/g or more), intermediate (5-5.5 μg/g), and low (2.5 μg/g or less) tooth lead levels for two socioeconomic groups (manual vs. non-manual workers). Parents were intensively interviewed at home regarding parental interest and attitudes toward education and family characteristics and relationships. The early history of the child was then studied in school using tests of intelligence (WISC-R), educational attainment, attention, and other cognitive tasks. Teachers and parents completed the Conners behavior questionnaires. Results showed that intelligence and other psychological measures were strongly related to social factors, especially social grouping. Lead level was linked to a variety of factors in the home, especially the level of cleanliness, and to a lesser extent, maternal smoking. There was no statistically significant link between lead level and IQ or academic performance. However, when rated by teachers (but not by parents), there were small, reasonably consistent (but not statistically significant) tendencies for high-lead children to show more behavioral problems after the different social covariables were taken into account statistically. The Smith et al. (1983) study has much to recommend it: (1) a well-drawn sample of adequate size; (2) three tooth lead groupings based on well-defined classifications minimizing possible overlaps of

exposure groupings using whole tooth lead values, including quality-controlled replicate analyses comparisons for the same tooth and duplicate analyses comparisons across multiple teeth from the same child; (3) blood lead levels on a subset of 92 children (averaging 13.1 μg/dl), which correlated reasonably well with tooth lead levels ($r = 0.45$); (4) cross-stratified design of social groups; (5) extensive information on social covariates and exposure sources; and (6) statistical control for potentially confounding covariates in the analsyes of study results. However, one possible source of selection bias was that tooth donors had a significantly higher social status than non-donors. Thus, the reported results may be less generalizable to the lower socioeconomic working classes, where one might expect the effects of lead exposure to be greater (Yule and Lansdown, 1983).

Harvey et al. (1983) also recently reported that blood lead made no significant contribution to IQ decrements after appropriate allowance had been made for social factors. This study involved 189 children, average age 2.5 years and 15.5 μg/dl blood lead, of middle class workers from the inner city of Birmingham, England. The investigators utilized a wide range of behavioral measures of activity level and psychomotor performance. Strengths of this study are: (1) a well-drawn sample, (2) extensive evaluation of 15 confounding social factors, (3) a wide range of abilities evaluated, and (4) blind evaluations. However, evaluation of lead burden was based on only a single venous blood sample, so that exposure history was not documented as well as in the study by Smith et al. (1983). Nevertheless, a stronger correlation between IQ and blood lead levels was found in children of manual workers ($r = -0.32$) than in children of non-manual workers ($r = -0.06$), consistent with findings from the Yule and Lansdown (1983) study discussed below.

Yule et al. (1981) carried out a pilot study on the effects of low-level lead exposure on 85 percent of a population of 195 children aged 6-12 years, whose blood lead concentrations had been determined some nine months earlier as part of a European Economic Community survey. The blood lead concentrations ranged from 7 to 32 μg/dl, and the children were assigned to four quartiles encompassing the following values: 7 to 10 μg/dl; 11 to 12 μg/dl; 13 to 16 μg/dl; and 17 to 32 μg/dl. The tests of achievement and intelligence were similar to those used in the Lansdown et al. (1974) and Needleman et al. (1979) studies. There were significant associations between blood lead levels and scores on tests of reading, spelling, and intelligence, but not on mathematics (Yule et al., 1981). These differences in performance largely remained after age, sex, and father's occupation were taken into account. However, other potentially confounding social factors were not controlled in this study. Another paper by Yule et al. (1983) dealt with the results pertinent to attention deficits. While there were few differences between groups on the Rutter Scale, the summed scores on the Needleman questionnaire across the blood lead groupings approached significance ($p = 0.096$). Three of

the questionnaire items showed a significant dose-response function ("Day Dreamer," "Does not Follow Sequence of Direction," "Low Overall Functioning"). Nine of 11 items were highly correlated with children's IQ. Therefore, the Needleman questionnaire may be tapping IQ-related attention deficits as opposed to measures of conduct disorder and socially maladaptive behavior (Yule et al., 1983). The hyperactivity factors on the Conners and Rutter scales were reported to be related to blood lead levels (7-12 vs. 13-32 μg/dl), but the authors noted that caution is necessary in interpreting their findings in view of the crude measures of social factors available and differences between countries in diagnosing attention deficit disorders. Moreover, since the blood lead values reported were determined only once (nine months before psychological testing), earlier lead exposures may not be fully reflected and the reported blood lead levels cannot be accepted confidently as those with which any behavioral effects might be associated. Also, home environment and parental IQ and education were not evaluated.

Yule and Lansdown (1983) reported a second, better designed study with similar methods and procedures using 194 children living in a predominantly lower-middle-class area of London near a busy roadway. In this study, a lengthy structured interview yielded data on sources of exposure, medical history, and many potentially confounding variables. Parental IQ was also examined. In contrast to the first pilot study, no statistically significant relationships were found even before social class was controlled for in the statistical analyses. Still, the authors stated that there was some evidence of weak associations between lead level and intelligence in working-class groups but whether these are of a causal nature in either direction is unclear.

Two studies by Winneke and colleagues, the first a pilot study (Winneke et al., 1982a) and the second an extended study (Winneke et al., 1982b) discussed later, employed teeth lead analyses analogous to some of the above studies. In the pilot study, incisor teeth were donated by 458 children aged 7 to 10 years in Duisburg, Germany, an industrial city with airborne lead concentrations between 1.5 and 2.0 $\mu g/m^3$. Two extreme exposure groups were formed, a low-lead group with 2.4 μg/g mean tooth lead level (n = 26) and another, high-lead group with 7 μg/g mean tooth lead level (n = 16), and matched for age, sex, and father's occupational status. The two groups did not differ significantly on confounding covariates, except that the high-lead group showed more perinatal risk factors. Parental IQ and quality of the home environment were not among the 52 covariables examined. The authors found a marginally significant decrease ($p < 0.10$) of 5-7 IQ points and a significant decrease in perceptual-motor integration ($p < 0.05$), but no significant differences in hyperactivity as measured by the Conners Teachers' Questionnaire administered during testing. As with the Yule et al. (1981) study, the inadequacy of the background social measures (e.g., parental IQ, caregiving environment, and pica), and group differences in perinatal factors weaken this study.

None of the general population studies reviewed provide strong evidence for neuropsychologic deficits being associated with relatively low body lead burdens in non-overtly lead intoxicated children representative of general pediatric populations. All of the studies reporting statistically significant associations between cognitive (IQ) or other behavior (e.g., attentional) deficits have methodological weaknesses, especially inadequate control for confounding covariates such as parental IQ or socioeconomic status. On the other hand, in view of the consistent pattern of results from such studies showing relationships between lead and neuropsychologic deficits before major confounding variables are controlled for, one cannot completely rule out the possibility that lead may be contributing to the observed deficits, especially given the cross-sectional design used in such studies (see Appendix 12-C introduction). The findings of no significant associations between lead and cognitive/behavioral deficits in several recently reported studies (generally controlling better for confounding variables) may not be incompatible with this possibility, in view of the latter studies apparently having evaluated children with lead body burdens likely generally lower than the former studies reporting at least suggestive evidence for lead effects on cognitive and behavioral functions.

12.4.2.2.2.3 Smelter area studies. These studies evaluated children with elevated lead exposures associated with residence in close proximity to lead emitting smelters.

For example, Lansdown et al. (1974) reported a relationship between blood lead level in children and the distance they lived from lead-processing facilities, but no relationship between blood lead level and mental functioning. However, only a minority of the lead-exposed cohort had blood lead levels over 40 μg/dl. Furthermore, this study failed to consider adequately social factors such as socioeconomic status.

In another study, Landrigan et al. (1975) found that lead-exposed children living near an El Paso, Texas, smelter scored significantly lower than matched controls on measures of performance IQ and finger-wrist tapping. The control children in this study were, however, not well matched by age or sex to the lead-exposed group, although the results remained statistically significant after adjustments were attempted for age differences. McNeil and Ptasnik (1975) found negative results in another sample of children living near the same lead smelter in El Paso who were generally comparable medically and psychologically to matched controls living elsewhere in the same city, except for the direct effects of lead (blood lead level, free erythrocyte protoporphyrin levels, and X-ray findings). An extensive critique of these two studies made by another expert committee (see Appendix 12-D) found that no reliable conclusions could be based on either of the two El Paso smelter studies in view of various methodological and other problems affecting the conduct of the studies.

A later study by Ratcliffe (1977) of children living near a battery factory in Manchester, England, found no relation between their blood levels taken at two years of age (28 µg/dl vs. 44 µg/dl in low- vs. high-lead groups) and testing done at age five on the Griffiths Mental Development Scales, the Frostig Developmental Test of Visual Perception, a pegboard test, or a behavioral questionnaire. The differences in scores, although small, favored the low-lead exposure children, i.d., they had somewhat better scores than the higher exposure group. The failure to repeat blood lead assays at age five weakens this otherwise adequate study; potentially higher blood lead levels occurring after age two among control children may have lessened exposure differences between the low- and high-lead groups.

Winneke et al. (1982b) carried out a study which involved 115 children aged 9.4 years living in the lead smelter town of Stolberg. Tooth lead ($\bar{X}$ = 6.16 ppm, range = 2.0-38.5 ppm) and blood lead levels ($\bar{X}$ = 13.4 µg/dl; range = 6.8-33.8 µg/dl were significantly correlated ($r = 0.47$; $p < 0.001$) for the children studied. Using stepwise multiple regression analysis, the authors found significant ($p < 0.05$) or marginally significant ($p < 0.10$) associations between tooth lead levels and measures of perceptual-motor integration, reaction time performance, and four behavioral rating dimensions, including distractibility. This was true even after taking into account age, sex, duration of labor at birth, and socio-heredity background as covariates. However, the proportion of explained variance due to lead never exceeded 6 percent for any of these outcomes, and no significant association was found between tooth lead and WISC verbal-IQ after the effects of socio-hereditary background were eliminated.

The above smelter area studies, again, do not provide strong evidence for cognitivie or behavior deficits being associated with lead exposure in nonovertly lead exposed children. At the same time, the possibility of such deficits being associated with lead exposure in apparently asymptomatic children cannot be ruled out, either, given the overall pattern of results obtained with the cross sectional study design typically employed (see Appendix 12-C introduction).

Several studies have also reported significant associations between hair lead levels and behavioral or cognitive testing endpoints (Pihl and Parkes, 1977; Hole et al., 1979; Hansen et al., 1980; Capel et al., 1981; Ely et al., 1981; Thatcher et al., 1982a,b; Marlowe et al., 1982, 1983; Marlowe and Errera, 1982). Measures of hair lead are easily contaminated by external exposure and are generally questionable in terms of accurately reflecting internal body burdens (see Chapter 9). Such data, therefore, cannot be credibly used to evaluate relationships between absorbed lead and nervous system effects and are not discussed further.

12.4.2.2.2.4 Studies of mentally retarded or behaviorally abnormal children. Other studies, of mentally retarded or autistic individuals and infants, have shown such abnormal populations to have somewhat higher lead levels than the control groups (Beattie et al., 1975;

David et al., 1972, 1976, 1979a,b, 1982a,b, 1983; Moore et al., 1977). However, whether disorders such as mental retardation, hyperactivity, autism, etc. are the causes or the effects of lead exposure is a difficult issue to resolve, and most of the studies cited employed study designs not capable of achieving such resolution. Still, results of at least one study (David et al., 1983) indicate that chelation therapy leading to reduced lead levels resulted in some improvement in behavior among a group of retarded individuals, suggesting that lead may contribute to deviant behavior patterns among such behaviorally abnormal populations, even if lead was not the key etiological factor originally causing the retardation or other behavioral abnormalities.

12.4.2.2.2.5 Electrophysiological studies of lead effects in children. In addition to studies using psychometric and behavioral testing approaches, electrophysiological studies of CNS lead neurotoxicity in non-overtly lead-intoxicated children have been conducted.

Burchfiel et al. (1980) used computer-assisted spectral analysis of a standard EEG examination on 41 children from the Needleman et al. (1979) study and reported significant EEG spectrum differences in percentages of low-frequency delta activity and in alpha activity in spontaneous EEGs of the high-lead children. Percentages of alpha and delta frequency EEG activity and results for several psychometric and behavioral testing variables (e.g., WISC-R full-scale IQ and verbal IQ, reaction time under varying delay, etc.) for the same children were then employed as input variables (or "features") in direct and stepwise discriminant analyses. The separation determined by these analyses for combined psychological and EEG variables ($p < 0.005$) was reported to be strikingly better than the separation of low-lead from high-lead children using either psychological ($p < 0.041$) or EEG ($p < 0.079$) variables alone. Unfortunately, no dentine lead or blood lead values were reported for the specific children from the Needleman et al. (1979) study who underwent the EEG evaluations reported by Burchfiel et al. (1980), and making it impossible to estimate lead-exposure levels associated with observed EEG effects. (See also Appendix 12-C).

The relationship between low-level lead exposure and neurobehavioral function (including electrophysiological responses) in children aged 13-75 months was extensively explored in another study, conducted at the University of North Carolina in collaboration with the U.S. Environmental Protection Agency. Psychometric evaluation (Milar et al., 1980, 1981a) revealed lower IQ scores for children with elevated blood lead levels of 30 µg/dl or higher compared with children with levels under 30 µg/dl, but the observed IQ deficits were confounded by poorer home caregiver environment scores in children with elevated blood lead levels (Milar et al., 1980); and no relationship between blood lead and hyperactive behavior (as indexed by standardized playroom measures and parent-teacher rating scales) was observed in these children (Milar et al., 1981a). On the other hand, electrophysiological assessments, including

analyses of slow cortical potentials during sensory conditioning (Otto et al., 1981) and EEG spectra (Benignus et al., 1981), did provide evidence of CNS effects of lead in the same children. In contrast to psychometric and behavioral findings, a significant linear relationship between blood lead (ranging from 6 to 59 µg/dl) and slow wave voltage (SW) was observed (Otto et al., 1981) as depicted in Figure 12-3. Analyses of quadratic and cubic trends in SW voltage, moreover, did not reveal any evidence of a threshold for this effect. The slope of the blood lead x SW voltage function, however, varied systematically with age. No effect of blood lead on EEG power spectra or coherence measures was observed, but the relative amplitude of synchronized EEG between left and right hemispheres (gain spectra) increased relative to blood lead levels (Benignus et al., 1981). A significant cubic trend for gain between the left and right parietal lobes was found with a major inflection point at 15 µg/dl. This finding suggests that EEG gain is altered at blood lead levels as low as 15 µg/dl, although the clinical and functional significance of this measure has not been established. A follow-up study of slow cortical potentials and EEG spectra in a subset (28 children aged 35 to 93 months) of the original sample was carried out two years later (Otto et al., 1982). Slow wave voltage during sensory conditioning again varied as a linear function of blood lead, even though the mean lead level had declined by 11 µg/dl (from 32.5 µg/dl to 21.1 µg/dl). The similarity of SW results obtained at initial and follow-up assessments suggests that the observed alterations in this parameter of CNS function are persistent, despite a significant decrease in the mean blood lead level during the two-year interval.

Results of the neurobehavioral study and two-year follow-up described above are important for several reasons. First, no significant relationship between child IQ and EEG measures was found in the initial (Benignus et al., 1981; Otto et al., 1981) or follow-up study. SW voltage and EEG gain thus appear to provide CNS indices of lead exposure effects that may be both more sensitive than and independent of standardized psychometric measures used in other studies. Electrophysiological measures such as these hold considerable promise as indicators of CNS function that are free of cultural bias and other linguistic and motor constraints attendant to traditional paper-and-pencil or behavioral tests. Observation of a linear relationship between SW voltage and blood lead within a range of 6 to 59 µg/dl, without evidence of any threshold effect level, is also provocative, particularly in view of the apparent persistence of the effect over a two-year interval. The inflection point in the EEG gain function at 15 µg/dl provides additional evidence of the effect of lead exposure of CNS function in young children at levels considerably below those previously considered to be safe (30 µg/dl). Interpretation of these electrophysiological data, however, must be carefully tempered in view of: (1) SW voltage and EEG gain are both experimental measures, the clinical and functional significance of which is presently unknown; (2) estimated effective blood lead levels associated with the EEG effects are somewhat probalematic because the effects might have resulted

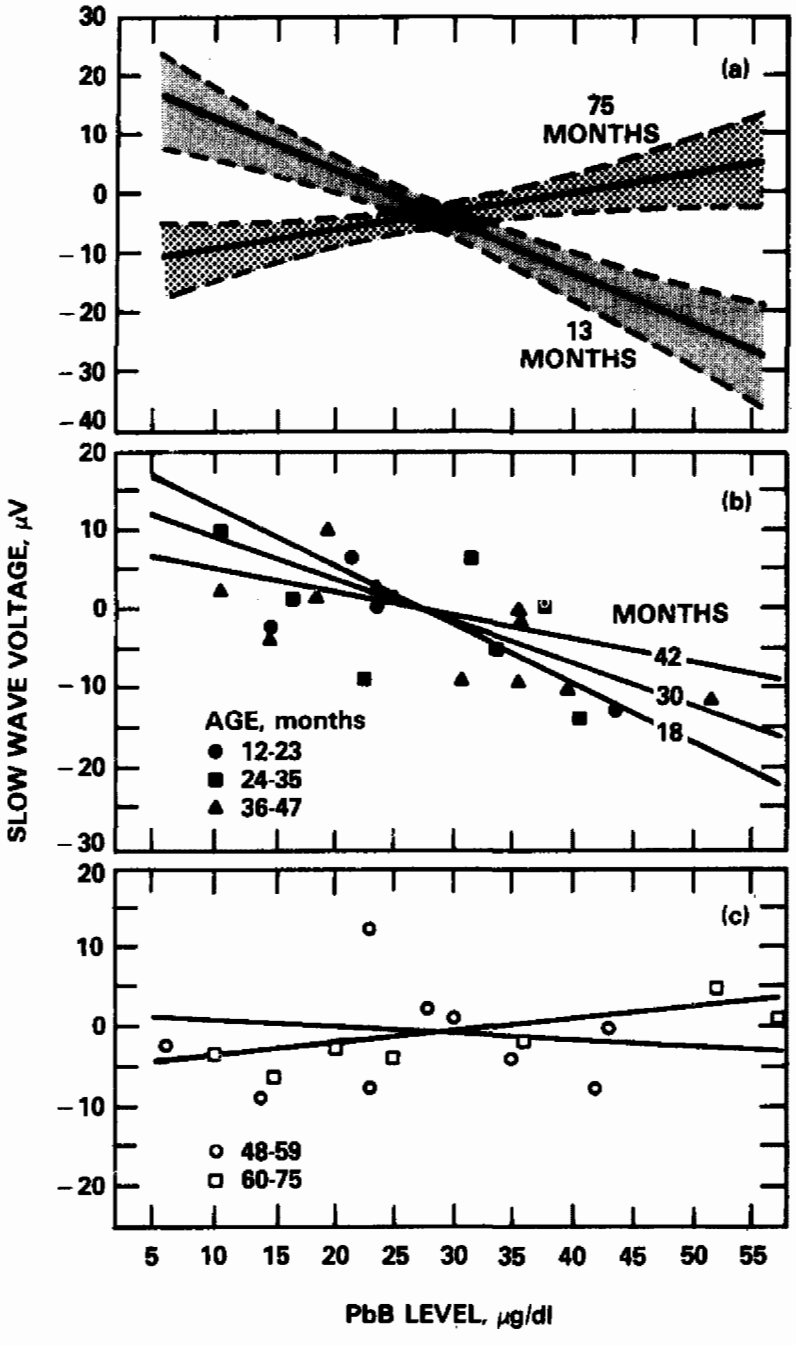

Figure 12-3. (a) Predicted SW voltage and 95% confidence bounds in 13- and 75-month-old children as a function of blood lead level. (b) Scatter plots of SW data from children aged 13-47 months with predicted regression lines for ages 18, 30, and 42 months. (c) Scatter plots for children aged 48-75 months with predicted regression lines for ages 54 and 66 months. These graphs depict the linear interaction of blood lead and age.

Source: Otto et al. (1981).

from higher blood lead levels prior to the reported studies; and (3) the study sample was relatively small (n = 43 for the original and 28 for the follow-up SW analyses). In view of these caveats, these findings need to be replicated in an independent sample. Nevertheless, they provide clear evidence of altered CNS functioning being associated with relatively low level lead exposure of non-overtly lead intoxicated children and at least lead levels likely well below 30 μg/dl.

The adverse effects of lead on peripheral nerve function in children remain to be considered. Lead-induced peripheral neuropathies, although often seen in adults after prolonged exposures, are rare in children. Several articles (Anku and Harris, 1974; Erenberg et al., 1974; Seto and Freeman, 1964), however, describe case histories of children with lead-induced peripheral neuropathies, as indexed by electromyography, assessment of nerve conduction velocity, and observation of other overt neurological signs, such as tremor and wrist or foot drop. Frank neuropathic effects have been observed at blood lead levels of 60 to 80 μg/dl (Erenberg et al., 1974). In other cases, signs indicative of peripheral neuropathy have been reported to be associated with blood lead values of 30 μg/dl. In these latter cases, however, lead lines in long bones suggest probable past exposures leading to peak blood lead levels at least as high as 40 to 60 μg/dl and probably in excess of 60 μg/dl (based on the data of Betts et al., 1973). In each of these case studies, some, if not complete, recovery of affected motor functions was reported after treatment for lead poisoning. A tentative association has also been hypothesized between sickle cell disease and increased risk of peripheral neuropathy as a consequence of childhood lead exposure. Half of the cases reported (10 out of 20) involved inner-city black children, several with sickle cell anemia (Anku and Harris, 1974; Feldman et al., 1973; Lampert and Schochet, 1968; Seto and Freeman, 1964; Imbus et al., 1978). In summary, (1) evidence exists for frank peripheral neuropathy in children, and (2) such neuropathy can be associated with blood lead levels at least as low as 60 μg/dl and, possibly, as low as 40-60 μg/dl.

Further evidence for lead-induced peripheral nerve dysfunction in children is provided by the data from two studies by Feldman et al. (1972, 1977) of inner city children and from a study by Landrigan et al. (1976) of children living in close proximity to a smelter in Idaho. The nerve conduction velocity results from this latter study are presented in Figure 12-4 in the form of a scatter diagram relating peroneal nerve conduction velocities to blood lead levels. No clearly abnormal conduction velocities were observed, although a statistically significant negative correlation was found between peroneal NCV and blood lead levels ($r = -0.38$, $p < 0.02$ by one-tailed t-test). These results, therefore, provide evidence for significant slowing of nerve conduction velocity (and, presumably, for advancing peripheral neuropathy as a function of increased blood lead levels), but do not allow clear statements to be made regarding a threshold for pathologic slowing of NCV.

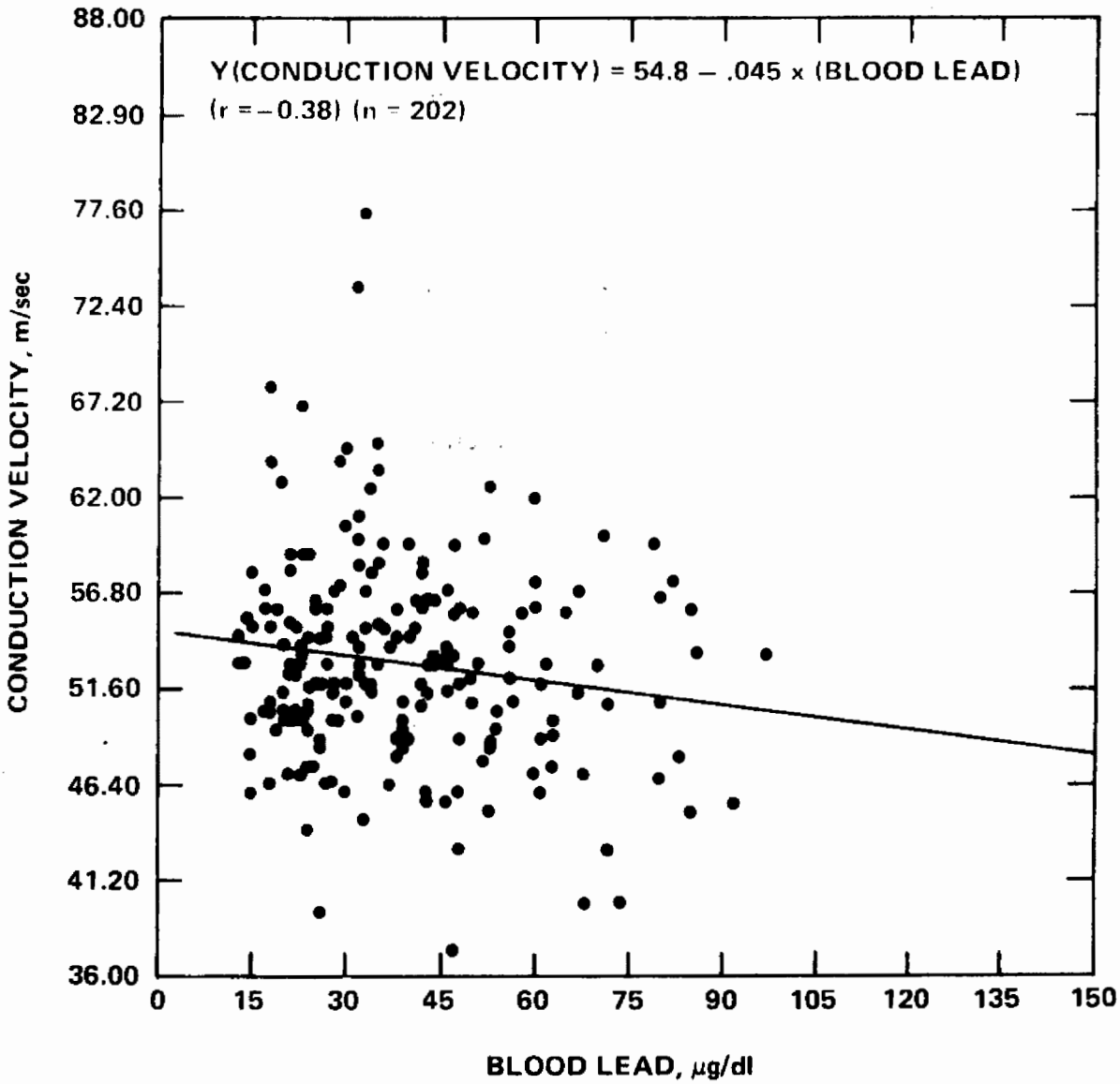

Figure 12-4. Peroneal nerve conduction velocity versus blood lead level, Idaho, 1974.

Source: Landrigan et al. (1976).

12.4.3 Animal Studies

The following sections focus on recent experimental studies of lead effects on behavioral, morphological, physiological, and biochemical parameters of nervous system development and function in laboratory animals. Several basic areas or issues are addressed: (1) behaviorial toxicity, including the question of critical exposure periods for concurrent induction or later expression of behavioral dysfunction in motor development, learning performance, and social interactions; (2) alterations in morphology, including synaptogenesis, dendritic development, myelination, and fiber tract formation; (3) perturbations in various electrophysiological parameters, e.g., ionic mechanisms of neurotransmission or conduction velocities in various tracts; (4) disruptions of biochemical processes such as energy metabolism and chemical neurotransmission; (5) the persistence or reversibility of the above types of effects beyond the cessation of external lead exposure; and (6) the issue of "threshold" for neurotoxic effects of lead.

Since the initial description of lead encephalopathy in the developing rat (Pentschew and Garro, 1966), considerable effort has been made to define more closely the extent of nervous system involvement at subencephalopathic levels of lead exposure. This experimental effort has focused primarily on exposure of the developing organism. The interpretation of a large number of studies dealing with early *in vivo* exposure to lead has, however, been made difficult by variations in certain important experimental design factors across available studies.

One of the more notable of the experimental shortcomings of some studies has been the occurrence of undernutrition in experimental animals (U.S. Environmental Protection Agency, 1977). Conversely, certain other studies of lead neurotoxicity in experimental animals have been confounded by the use of nutritionally fortified diets, i.e., most commercial rodent feeds (Michaelson, 1980). In general, deficiencies of certain minerals result in increased absorption of lead, whereas excesses of these minerals result in decreased uptake (see Chapter 10). Commercial feeds may also be contaminated by variable amounts of heavy metals, including as much as 1.7 ppm of lead (Michaelson, 1980). Questions have also been raised about possible nutritional confounding due to the acetate radical in lead acetate solutions, which are often used as the source of lead exposure in experimental animal studies (Barrett and Livesey, 1982).

Another important factor that varies among many studies is the route of exposure to lead. Exposure of the suckling animal via the dam would appear to be the most "natural" method, yet may be confounded by lead-induced chemical changes in milk composition. On the other hand, intragastric gavage allows one to determine precisely the dose and chemical form of administered lead, but the procedure is quite stressful to the animal and does not necessarily reflect the actual amount of lead absorbed by the gut. Injections of lead salts (usually

performed intraperitoneally) do not mimic natural exposure routes and can be complicated by local tissue calcinosis at the site of repeated injections.

Another variable in experimental animal studies that merits attention concerns species and strains of experimental subjects used. Reports by Mykkänen et al. (1980) and Overmann et al. (1981) have suggested that hooded rats and albino rats may differ in their sensitivity to the toxic effects of lead, possibly because of differences in their rates of maturation and/or rates of lead absorption. Such differences may account for variability of lead effects and exposure-response relationships between different species as well.

Each of the above factors may lead to widely variable internal lead burdens in the same or different species exposed to roughly comparable amounts of lead, making comparison and interpretation of results across studies difficult. The force of this discussion, then, is to emphasize the importance of measurements of blood and tissue concentrations of lead in experimental studies. Without such measures, attempts to formulate dose-response relationships are futile. This problem is particularly evident in later sections dealing with the morphological, biochemical, and electrophysiological aspects of lead neurotoxicity. In vitro studies accorded attention in those sections, in contrast to in vivo studies, are of limited relevance in dose-response terms. The in vitro studies, however, provide valuable information on basic mechanisms underlying the neurotoxic effects of lead.

The following sections discuss and evaluate the most recent studies of nervous system involvement at subencephalopathic exposures to lead. Older studies reviewed in the previous Air Quality Criteria Document for Lead (U.S. Environmental Protection Agency, 1977) are cited as needed to illustrate particular points but, in general, the discussion below focuses on more recent work.

12.4.3.1 Behavioral Toxicity: Critical Periods for Induction and Expression of Effects. The 1977 EPA review (U.S. Environmental Protection Agency, 1977) of animal behavioral studies and a number of articles since then (e.g., Shigeta et al., 1977; Zenick et al., 1979; Crofton et al., 1980; Kimmel, 1983) have pointed to the perinatal period of ontogeny as a particularly critical time for the induction of behavioral effects due to lead exposure. Such findings are consistent with the general pattern of development of the nervous system in the experimental animals that have been investigated (see Reiter, 1982) and are reviewed in some detail in the ensuing sections of this chapter.

Alterations in the behavior of rats exposed after weaning or after maturation have also been reported (Angell and Weiss, 1982; Cory-Slechta and Thompson, 1979; Cory-Slechta et al., 1981; Donald et al., 1981; Geist and Mattes, 1979; Lanthorn and Isaacson, 1978; Nation et al., 1982; Shapiro et al., 1973). These findings stand in contrast to results from other studies showing some effects in rats as being produced only by early perinatal exposure (e.g., Brown,

1975; Brown et al., 1971; Padich and Zenick, 1977; Shigeta et al., 1977; Snowdon, 1973). Nevertheless, behavioral effects of relatively low-level exposure to lead have also been noted in adult subjects of other species, including pigeons (Barthalmus et al., 1977; Dietz et al., 1979) and fish (Weir and Hine, 1970), and the effects of lead exposure during adulthood are not to be dismissed as inconsequential, although the present evaluation focuses mainly on the effects of lead exposure early in development.

12.4.3.1.1 Development of motor function and reflexes. A variety of methods have been used to assess the effect of lead on the ability of experimental animals to respond appropriately, either by well defined motor responses or gross movements, to a defined stimulus. Such responses have been variously described as reflexes, kineses, taxes, and "species-specific" behavior patterns. The air righting reflex, which refers to the ability to orient properly with respect to gravity while falling through the air and to land on one's feet, is only one of several commonly used developmental markers of neurobehavioral function (Tilson and Harry, 1982). Overmann et al. (1979) found that development of this particular reflex was slowed in rat pups exposed to lead via their dams (0.02 or 0.1 percent lead as lead acetate in the dams' drinking water). However, neither the auditory startle reflex nor the ability to hang suspended by the front paws was affected.

Grant et al. (1980) exposed rats indirectly to lead in utero and during lactation through the mothers' milk and, after weaning, directly through drinking water containing the same lead concentrations their respective dams had been given. In addition to morphological and physical effects [see Sections 12.5, 12.6, and 12.11 for discussions of this work as reported by Kimmel et al. (1980), Fowler et al. (1980), Faith et al. (1979), and Luster et al. (1978)], there were delays in the development of surface righting and air righting reflexes in subjects exposed under the 0.005 and 0.025 percent lead conditions; other reflexive patterns showed no effect. The median blood lead concentration for the 0.005-percent subjects at postnatal day (PND) 11 was 35 µg/dl; the median brain lead concentration was 0.07 µg/g. Locomotor development generally showed no significant alteration due to lead exposure. Body weight was significantly depressed for the most part in the 0.005- and 0.025-percent pups.

The ontogeny of motor function was also investigated by Overmann et al. (1981). Exposure of pups to lead was limited to the period from parturition to weaning and occurred through adulteration of the dams' drinking water with lead acetate (0.01 or 0.1 percent lead acetate). The development of swimming performance was assessed on alternate days from PND 6 to 24. No alterations in swimming ability were found. Rotorod performance was also tested at PND 21, 30, 60, 90, 150, and 440. Overall, the ability to remain on a rotating rod was significantly impaired ($p < 0.01$) at 0.1 percent and tended to be impaired ($0.10 > p > 0.05$) at 0.1 percent (blood lead values were not reported). However, data for individual days were statistically

significant only on PND-60 and 150. An adverse effect of lead exposure on rotorod performance at PND 30-70 was also found in an earlier study by Overmann (1977) at a higher exposure level of 30 mg/kg lead acetate by intubation (average PbB value at PND 21 was 173.5 ± 32.0 µg/dl). At blood lead concentrations averaging 33.2 ± 1.4 µg/dl, however, performance was not impaired. Moreover, other studies using rotorods at average blood lead concentrations of approximately 61 µg/dl (Zenick et al., 1979) and 30 to 48 µg/dl (Grant et al., 1980) have not found significant effects of lead on such performance when tested at PND 21 and 45, respectively. Comparisons between studies are confounded by differences in body weight and age at time of testing and by differences in speed and size of the rotorod apparatus (Zenick et al., 1979).

Delays in the development of gross activity in rat pups have been reported by Crofton et al. (1980) and by Jason and Kellogg (1981). It should be noted that very few studies have been designed to measure the rate of development of activity. Ideally, subjects should be assessed daily over the entire period of development in order to detect any changes in the rate at which a behavior pattern occurs and matures. In the study by Crofton et al. (1980), photocell interruptions by pups as they moved through small passageways into an "exploratory cage" adjacent to the home cage were automatically counted on PND 5 to 21. Pups exposed in utero through the dams' drinking water (0.01 percent solution of lead as lead chloride) lagged controls by approximately one day in regard to characteristic changes in daily activity count levels starting at PND 16. (Blood lead concentrations at PND 21 averaged 14.5 ± 6.8 µg/dl for representative pups exposed to lead in utero and 4.8 ± 1.5 µg/dl for controls.) Another form of developmental lag in gross activity around PND 15-18, as measured in an automated activity chamber, was reported by Jason and Kellogg (1981). Rats were intubated on PND 2-14 with lead at 25 mg/kg (PbB = 50.07 ± 5.33 µg/dl) and 75 mg/kg (PbB = 98.64 ± 9.89 µg/dl). In this case, the observed developmental lag was in the characteristic decrease in activity that normally occurs in pups at that age (Campbell et al., 1969; Melberg et al., 1976); thus, lead-exposed pups were significantly more active than control subjects at PND 18.

One question that arises when ontogenetic effects are discovered concerns the possible contribution of the lead-exposed dam to her offsprings' slowed development through, for example, reduced or impaired maternal care giving behavior. A detailed assessment of various aspects of maternal behavior in chronically lead-exposed rat dams by Zenick et al. (1979), discussed more fully in Section 12.4.3.1.4, and other studies using cross-fostering techniques (Crofton et al., 1980; Mykkänen et al., 1980) suggest that the deleterious effects observed in young rats exposed to lead via their mothers' milk are not ascribable to alterations in the dams' behavior toward their offspring. Chronically lead-exposed dams may, if anything, tend to respond adaptively to their developmentally retarded pups by, for example, more quickly retrieving them to the nest (Davis, 1982).

12.4.3.1.2 Locomotor activity. The spontaneous activity of laboratory animals has been measured frequently and in various ways as a behavioral assay in pharmacology and toxicology (Reiter and MacPhail, 1982). Such activity is sometimes described as gross motor activity or exploratory behavior, and is distinguished from the motor function tests noted in the previous section by the lack of a defined eliciting stimulus for the activity. With reports of hyperactivity in lead-exposed children (see Section 12.4.2), there has naturally been considerable interest in the spontaneous activity of laboratory animals as a model for human neurotoxic effects of lead (see Table 12-2). As the 1977 review (U.S. Environmental Protection Agency, 1977) of this material demonstrated, however, and as other reviews (e.g., Jason and Kellogg, 1980; Michaelson, 1980; Mullenix, 1980) have since confirmed, the use of activity measures as an index of the neurotoxic effects of lead has been fraught with difficulties.

First, there is no unitary behavioral endpoint that can be labeled "activity." Activity is, quite obviously, a composite of many different motor actions and can comprise diverse behavior patterns including (in rodents) ambulation, rearing, sniffing, grooming, and, depending on one's operational definition, almost anything an animal does. These various behavior patterns may vary independently, so that any gross measure of activity which fails to differentiate these components will be susceptible to confounding. Thus, different investigators' definitions of activity are critical to interpreting and comparing these findings. When these definitions are sufficiently explicit operationally (e.g., activity as measured by rotations of an "activity wheel"), they are frequently not comparable with other operational definitions of activity (e.g., movement in an open field as detected by photocell interruptions). Moreover, empirical comparisons show that different measures of activity do not necessarily correlate with one another quantitatively (e.g., Copobianco and Hamilton, 1976; Tapp, 1969).

In addition to these rather basic difficulties, activity levels are influenced greatly by numerous variables such as age, sex, estrous cycle, time of day, novelty of environment, and food deprivation. If not controlled properly, any of these variables can confound measurements of activity levels. Also, nutritional status has been a frequent confounding variable in experiments examining the neurotoxic effects of lead on activity (see the review by U.S. Environmental Protection Agency, 1977; Jason and Kellogg, 1980; Michaelson, 1980). In general, it appears that rodents exposed neonatally to sufficient concentrations of lead experience undernutrition and subsequent retardation in growth; and, as Loch et al. (1978) have shown, retarded growth *per se* can induce increased activity of the same types that were attributed to lead alone in some earlier studies.

In view of the various problems associated with the use of activity measures as a behavioral assay of the neurotoxic effects of lead, the discrepant findings summarized in Table 12-2 should come as no surprise. Until the measurement of "activity" can be better

TABLE 12-2. EFFECTS OF LEAD ON ACTIVITY IN RATS AND MICE

Increased	Decreased	Age-dependent, qualitative, mixed or no change
Driscoll and Stegner (1978)	Driscoll and Stegner (1976)	Barrett and Livesey (1982)
Golter and Michaelson (1975)	Flynn et al. (1979)	Brown (1975)
Kostas et al. (1976)	Gray and Reiter (1977)	Crofton et al. (1980)
Overmann (1977)	Reiter et al. (1975)	Cutler (1977)
Petit and Alfano (1979)	Verlangieri (1979)	Dolinsky et al. (1981)
Sauerhoff and Michaelson (1973)		Dubas and Hrdina (1978)
Silbergeld and Goldberg (1973, 1974a,b)		Geist and Balko (1980)
Weinreich et al. (1977)		Geist and Praed (1982)
Winneke et al. (1977)		Grant et al. (1980)
		Gross-Selbeck and Gross-Selbeck (1981)
		Hastings et al. (1977)
		Jason and Kellogg (1981)
		Kostas et al. (1978)
		Krehbiel et al. (1976)
		Loch et al. (1978)
		Minsker et al. (1982)
		Mullenix (1980)
		Ogilvie and Martin (1982)
		Rafales et al. (1979)
		Schlipköter and Winneke (1980)
		Sobotka and Cook (1974)
		Sobotka et al. (1975)
		Zimering et al. (1982)

standardized, there appears to be little basis for comparing or utility in further discussing the results of studies listed in Table 12-2.

12.4.3.1.3 Learning ability. When animal learning studies related to the neurotoxic effects of lead were reviewed in 1977 (U.S. Environmental Protection Agency, 1977), a number of criticisms of existing studies were noted. A major limitation of early work in this field was the lack of adequate information on the exposure regimen (dosage of lead, how precisely administered, timing of exposure) and the resulting body burdens of lead in experimental subjects (concentrations of lead in blood, brain, or other tissue; time course of blood or tissue lead values, etc.). A review of studies appearing since 1977 reveals a notable improvement in this regard. A number of more recent studies have also attempted to control for the confounding factors of litter effects and undernutrition--variables that were generally not controlled in earlier studies.

Unfortunately, other criticisms are still valid today. The reliability and validity of behavioral assays remain to be established adequately, although progress is being made. The reliability of a number of common behavioral assays for neurotoxicity is currently being determined by several independent U.S. laboratories (Kimmel et al., 1982). The results of this program should help standardize some behavioral testing procedures and perhaps create some reference methods in behavioral toxicology. Also, as well-described studies are replicated within and between laboratories, the reliability of certain experimental paradigms for demonstrating neurotoxic effects is effectively established.

Some progress is also being made in dealing with the issue of the validity of animal behavioral assays. As the neurological and biochemical mechanisms underlying reliable behavioral effects become better understood, the basis for extrapolating from one species to another becomes stronger and more meaningful. An awareness of different species' phylogenetic, evolutionary, and ecological relationships can also help elucidate the basis for comparing behavioral effects in one species with those observed in another (Davis, 1982).

Tables 12-3 and 12-4 summarize exposure conditions, testing conditions, and results of a number of recent studies of animal learning (see U.S. Environmental Protection Agency, 1977, for a summary of earlier studies). Some general issues emerge from an examination of these studies. One point of obvious interest is the lowest level of exposure at which behavioral effects are clearly evident. Such a determination is best done on a species-by-species basis. Rats seem to be the species of choice for the great majority of the behavioral studies, despite the concerns that have repeatedly been expressed concerning the appropriateness of this species as a subject for behavioral investigation (e.g., Lockard, 1968, 1971; Zeigler, 1973). Of the studies not obviously confounded by nutritional or litter effects, those by Winneke et al. (1977, 1982c) and by Cory-Slechta and Thompson (1979) report alterations in

TABLE 12-3. RECENT ANIMAL TOXICOLOGY STUDIES OF LEAD EFFECTS ON LEARNING IN RODENT SPECIES

Reference	Experimental animal (species or strain)	Lead exposure: Pb conc. (medium)	Lead exposure: period (route)	Treatment groups (n)	Litters per group	Tissue lead (age measured)	Age at testing	Testing paradigm (task)	Non-behavioral effects	Behavioral results
Hastings et al. (1977)	Rat (L-E)	0.01 or 0.05% (water)	PND 0-21 (dam's milk)	C (12) Pb_1 (12) Pb_2 (12)	Random selection from 9 litters	PbB (20 d): C: 11 µg/dl Pb_1: 29 Pb_2: 42 (60 d): C: 4 Pb_1: 5 Pb_2: 9	~90-186 d	Operant (successive brightness discrim.)	None	No sig. differences between Pb-Ss and C-Ss in learning original or reversed discrim. task.
Overmann (1977)	Rat (L-E)	10, 30, or 90 mg/kg (gavage)	PND 3-21 (direct)	C Pb_1 12- Pb_2 25 Pb_3 ea.	?	PbB (21 d) C: 15 µg/dl Pb_1: 33.2 Pb_2: 173.5 Pb_3: 226.1	26-29 d 67-89 d 79-101 d 83-105 d 95-117 d	Aversive conditioning (1) active 2) passive) Operant (inhibit response) E-maze (discrim.: 1) spatial 2) tactile 3) visual)	None	Pb_3-Ss sig. slower in acquisition and extinction of active avoidance response; no sig. diffs. for passive avoidance. All Pb groups failed to inhibit responses as well as C-Ss. No sig. diffs. on E-maze tasks, except $Pb_{2,3}$-Ss sig. worse than C-Ss when on tactile discrim.
Padich and Zenick (1977)	Rat (CD)	375 mg/kg (water)	Preconception to a) Weaning (via dam) or b) termination (via dam and direct); or Weaning to termination (direct only)	0-0 (10) 0-Pb (10) Pb-0 (10) Pb-Pb (10)	5 5 5 5	?	42-? d	Operant (FR 20)	Body wt. of Pb-Ss < 0-Ss from birth to weaning.	Pb-Pb group had sig. fewer rewarded responses even though responding at sig. higher rate.
Winneke et al. (1977)	Rat (W)	372 mg/kg (food)	Preconception - Testing (via dam and direct)	C (20) Pb (20)	? (random selection from 110 male pups)	PbB (~16 d): C: 1.7 µg/dl Pb: 26.6 (~190 d) Pb: 28.5	100-200 d	Lashley jumping stand (visual discrim. of stimulus: 1) orientation 2) size)	Body wt. of Pb-Ss > C-Ss; however, size of Pb-Ss litters < C-S litters.	Pb-Ss sig. slower to learn size discrimination; no diff. between Pb and C groups on orientation discrim. (a relatively easy task).

TABLE 12-3. (continued)

Reference	Experimental animal (species or strain)	Lead exposure: Pb conc. (medium)	Lead exposure: period (route)	Treatment groups (n)	Litters per group	Tissue lead (age measured)	Age at testing	Testing paradigm (task)	Non-behavioral effects	Behavioral results
Dietz et al. (1978)	Rat Expt. 1(L-E)	200 mg/kg (gavage)	PND 3-30 (direct)	C (6) Pb (7)	2, split	?	3 mo or 21 mo	Operant (minimum 20-sec pd. between bar-presses)	None	Short IRTs (≤4 sec) more prevalent in Pb-Ss than in C-Ss, but did not result in different reward rates; Pb-Ss showed higher variability in response-rate under d-amphetamine treatment.
	Expt. 2(CD)	0.01% (water)	Preconception to termination (via dam until weaning, then direct)	C (4)* Pb (4)	?	?	8 mo		Pb-body wt. lower 1 wk. prior to test; C reduced to same wt. at test.	
Lanthorn & Isaacson (1978)	Rat (L-E)	0.27% (water)	Adult (direct)	C (4) Pb (6)	?	?	Adult	T-maze (1) spontan. alternation 2) light discrim. 3) spatial discrim.)	C-Ss pair-fed to control for loss of body wt.	Pb-Ss had sig. lower rate of spontaneous alternation; Pb-Ss sig. slower than C-Ss only on 1st spatial discrim. task.
Cory-Schlecta & Thompson (1979)	Rat (S-D)	(1) 0.005, (2) 0.03, or (3) 0.1% (water)	PND 20- (a) 70 or (b) 150 (direct)	1a: C (4)* Pb (5) 1b: C (4)* Pb (6) 2: C (3)* Pb (4) 3: C (4)* Pb (5)	random assignment	PbB (150 d): C: ~6 µg/dl 1a: ~3 1b: ~7 2: ~27 3: ~42	55-140 d	Operant (FI-30 sec)	None	Increased response rate and inter-S variability in groups $Pb_{1a,b}$ and Pb_2; decreased response rate in group Pb_3; effects in Pb_{1a} reversed after exposure terminated.
Cory-Schlecta et al. (1981)	Rat (S-D)	(1) 0.01 or (2) 0.03% (water)	PND 21-?	C (4) Pb_1 (5) Pb_2 (5)	random assignment	Brain-Pb (post-test): C: 14-26 ng/g Pb_1: 40-142 Pb_2: 320-1080	55-? d	Operant (minimum duration bar-press)	None	Pb groups impaired: decreased response durations; increased response latencies; failure to improve performance by external stimulus control.

*Weight-matched controls

TABLE 12-3. (continued)

Reference	Experimental animal (species or strain)	Lead exposure: Pb conc. (medium)	Lead exposure: period (route)	Treatment groups (n)	Litters per group	Tissue Lead (age measured)	Age at testing	Testing paradigm (task)	Non-behavioral effects	Behavioral results
Geist & Mattes (1979)	Rat (S-D)	0.001 or 0.0025% (water)	PND 23-termination (direct)	C (7) Pb_1 (7) Pb_2 (7)	?	?	58-? d	Hebb-Williams maze (find way to goal box)	None	Pb_1- and Pb_2-Ss made sig. more errors than C-Ss; Pb_2-Ss slower than C-Ss to traverse maze.
Flynn et al. (1979)	Rat (L-E) Expt. 1	0.25% (water)	Preconception - PND 22 (via dam)	C (8) Pb (10)	8 10	Brain-Pb (3 d): C: ~0 Pb: 0.174 µg/g (30-34 d): no sig. diffs.	?	Radial arm maze (spontaneous alternation)	Brain wts. of Pb-Ss < C-Ss; no other differences.	No sig. difference between Pb-Ss and C-Ss.
	Expt. 2	0.1% (watar), 225 mg/kg (gavage), 0.25% (water)	Preconception - Birth (via dam), Birth - Weaning (direct), Weaning - termination (direct)	C (12) Pb (12)	6 6	(75-76 d): C: 0.13 µg/g Pb: 1.85	49-58 d	Passive avoidance (remain in 1 of 2 compartments to avoid elect. shock)	None	No sig. difference in trials to criterion, but Pb-Ss made sig. fewer partial excursions from "safe" compartment.
	Expt. 3	same as above except 90 mg/kg (gavage)	same as above except stopped at PND 33	C (10) Pb (10)	4	see above	58-60 d	Shuttle-box signalled avoidance (move from one compartment to other to avoid elect. shock)	None	No sig. difference between Pb-Ss and C-Ss.
Petit & Alfano (1979)	Rat (L-E)	0.2 or 2% (food)	PND 1-25	C_i (22) C_e (22) Pb_{1_i} (22) Pb_{1_e} (22) Pb_{2_i} (22) Pb_{2_e} (22)	~7 each; split for "i" (isolation and "e" (enrichment) conditions	PbB (25 d): C: 2 µg/dl Pb_1: 331 Pb_2: 1297	66-115 d	Hebb-Williams maze (find way to goal box) Passive avoidance (remain in compartment to avoid shock)	Body wts. of Pb_2-Ss < C-Ss, Pb_1-Ss > C-Ss; gross toxicity in Pb_2-Ss; lower brain wts. in Pb-Ss	No sig. diff. between Pb- and C-Ss in maze learning; Isolation-reared Pb-Ss less successful than C_i-Ss on passive avoidance task; enrichment-reared Pb_1-Ss = C_e-Ss but Pb_{2_e}-Ss sig. worse on passive avoidance.

TABLE 12-3 (continued)

Reference	Experimental animal (species or strain)	Lead exposure: Pb conc. (medium)	Lead exposure: period (route)	Treatment groups (n)	Litters per group	Tissue lead (age measured)	Age at testing	Testing paradigm (task)	Non-behavioral effects	Behavioral results
Zenick et al. (1978)	Rat (CD)	500 mg/kg (water)	Preconception - Weaning (via dam)	C (10) Pb (10)	5 5	?	30-40 d 55-63 d	Water T-maze 1) black-white discrim. 2) shape discrim.	Body wt. of Pb-Ss < C-Ss from birth to 50 d.	On both discrim. tasks, Pb-Ss made sig. more errors with sig. shorter response
Zenick et al. (1979)	Rat (CD)	375 mg/kg (water)	Preconception to a) Weaning (via dam or b) termination (via dam and direct)	0-0 (?) Pb-0 (?) Pb-Pb (?)	5 5 5	?	42-? d	Operant (FI-1 min)	Body wt. of Pb-Ss < 0-Ss from birth to weaning.	Pb-Pb group had sig. fewer rewarded responses across sessions than Pb-0 or 0-0 groups.
Hastings et al. (1979)	Rat (L-E)	0.01 or 0.1% (water)	PND 0 - 21 (dam's milk)	C (23) Pb_1 (11) Pb_2 (13)	Random selection from 15 litters	PbB (20 d): C: 11 µg/dl Pb_1: 29 Pb_2: 65 Brain-Pb (20 d): C: 12.5 µg% Pb_1: 29 Pb_2: 65	120 d 270 d 330 d	(1) Operant (simult. vis. discrim.) (2) T-maze (success. vis. discrim.) (3) Operant (go/no-go task)	None	Pb_2-Ss sig. slower to reach criterion than C-Ss on simultaneous visual discrimination task; no sig. differences on successive and go/no-go discrim. tasks.
Schlipköter & Winneke (1980)	Rat (?) Expt. 1	0.23% (food)	Preconception - PND 120 (via dam and direct)	C (?) Pb_1 (18)	?	PbB all C: <5 µg/dl Pb_1 (120 d): 39.5 (8 mo): 12.0	7 mo	Lashley jumping stand (cue - size discrim.)	?	Sig. increase in error repetition by Pb_1-Ss.
	Expt. 2	0.075% (food)	a) Prenatal-7 mo (via dam and direct) b) Prenatal-Weaning (via dam)	C (10) Pb_{2a} (10) Pb_{2b} (10)	?	Pb_{2a}: (21 d) 29.2 (7 mo) 27.0 Pb_{2b}: (21 d) 29.2 (7 mo) 5.2	"	"	?	Non-sig. ($p < 0.10$) increase in error repetition by Pb_2-Ss.
	Expt. 3	------Same as Expt. 2------		C (14) Pb_{3a} (14) Pb_{3b} (14)	?	Pb_{3a}: (21 d) 29.9 (7 mo) 30.8 Pb_{3b}: (21 d) 29.9 (7 mo) 1.8	"	"	?	No sig. diffs. between Pb_3-Ss and C-Ss.
	Expt. 4	0.025 or 0.075% (food)	Prenatal - 7 mo (via dam and direct)	C (10) Pb_{4a} (10) Pb_{4b} (10)	?	(120 d) Pb_{4a}: 17.8 Pb_{4b}: 28.6	"	Water maze (spatial discrim.)	?	35% of Pb_4-Ss failed to reach criterion (vs. 10% C-Ss); 35% also failed retest after 1 wk (vs. 0% C-Ss).

TABLE 12-3. (continued)

Reference	Experimental animal (species or strain)	Lead exposure: Pb conc. (medium)	Lead exposure: period (route)	Treatment groups (n)	Litters per group	Tissue lead (age measured)	Age at testing	Testing paradigm (task)	Non-behavioral effects	Behavioral results
Gross-Selbeck & Gross-Selbeck (1981)	Rat F_1 (W)	0.5 g/kg (food)	Postweaning - termination (direct)	C (6) Pb (6)	?	PbB (~180 d): C: 6.2 µg/dl Pb: 22.7	Adult	Operant (DRH)	None	Both F_1 and F_2 (especially F_2) Pb-Ss had greater % rewarded responses than C-Ss, i.e., Pb-Ss bar-pressed at higher rate than C-Ss.
	F_2	"	Preconception - Weaning (via dam)	C (6) Pb (6)	?	(~110 d): C: 3.7 Pb: 4.6	3-4 mo	"	"	
Angell & Weiss (1982)	Rat (L-E)	0.1% (water)	PND 3-21 (dam's milk) and/or 21-130 (direct)	0-0 (20) 0-Pb (20) Pb-0 (24) Pb-Pb (24)	5, split 6, split	PbB(130d): 0-0: 2 µg/dl 0-Pb: 66 Pb-0: 9 Pb-Pb: 64	58-130 d	Operant (Mult FI-TO-FR-TO)	Pb-Pb Ss sig. lower body wt. postweaning	Groups exposed post-weaning (0-Pb, Pb-Pb) had longer Inter-Response Times; group exposed preweaning (Pb-0) had shorter IRTs.
Milar et al. (1981b)	Rat (L-E)	25, 100, or 200 mg/kg	PND 4-31 (direct)	C (10) Pb_1 (5) Pb_2 (4)	3 4 4	PbB (32 d) C: 5 µg/dl Pb_1: 26 Pb_2: 123	50 d	Operant (spatial alternation levers)	Pb_2-Ss sig. slower rate	No sig. differences between C-Ss and Pb-Ss.
Nation et al. (1982)	Rat (S-D)	10 mg/kg (food)	PND 100-termination (direct)	C (8) Pb (8)	?	?	156 d	Operant (conditioned suppression of responding on mult. VI schedule)	None	Presentation of tone associated with electrical shock disrupted steady-state responding more in PB-Ss than in C-Ss.
Winneke et al. (1982c)	Rat (W) Expt. 1	0.004, 0.012, or 0.037% (food)	Preconception - Testing (via dam and direct)	C(16) Pb_1 (16) Pb_2 (16) Pb_3 (16)	Random selection from 5-6 litters per condition	?	70-100 d	Shuttle-box signalled avoidance (move from one compartment to avoid elect. shock)	ALA-D at 90 d: C: 7.05 U/l Pb_1: 4.26 Pb_2: 1.92 Pb_3: 1.18	Expt. 1 Pb-Ss sig. faster than C-Ss to learn avoidance response.
	Expt. 2	-Continuation of Expt. 1-		C (10) Pb_2 (10) Pb_3 (10)	(females dropped; no Pb_1 group for Expt. 2)	?	190-250 d	Lashley jumping stand (size discrim.)		Expt. 2 Pb-Ss sig. slower than C-Ss to learn size discrim.

PRELIMINARY DRAFT

TABLE 12-3 (continued)

Reference	Experimental animal (species or strain)	Lead exposure: Pb conc. (medium)	Lead exposure: period (route)	Treatment groups (n)	Litters per group	Tissue lead (age measured)	Age at testing	Testing paradigm (task)	Non-behavioral effects	Behavioral results
Taylor et al. (1982)	Rat (CD)	0.0% or 0.02% (water)	Preconception - Weaning (via dam)	C (12) Pb_1 (16) C_2 (4) Pb_2 (4)	6* 8* 2* 2*	PbB (21 d) C: 3.7 µg/dl Pb_1: 38.2 Pb_2: 49.9	11 d	Runway (traverse alley to reach dam and dry suckle)	None	No sig. diffs. in acquisition of response, but both Pb groups sig. slower to extinguish when response no longer rewarded.
Kowalski et al. (1982)	Mouse (Wistar)	0.0002% (water)	Adult (direct)	C (16) Pb (16)	?	?	(13 d after start of exposure)	Water T-maze (spatial discrim.)	None	Pb-Ss made more errors than C-Ss; food deprivation exacerbated effect.
McLean et al. (1982)	Mouse (Swiss)	0.002 or 0.2% (water)	Adult (direct)	C (16) Pb_1 (16) Pb_2 (16)	?	?	(10 d after start of expos.)	Water T-maze (spatial discrim.)	None	Pb-Ss showed no improvement in performance compared to C-Ss.

*Inferred from information in report.

Abbreviations:

?	information not given in report
ALA-D	delta Aminolevulinic Acid Dehydrase
C	Control group
CD	substrain of Sprague Dawley
DRH	Differential Reinforcement of High response rates
F_1	1st Filial generation
F_2	2nd Filial generation
FI	Fixed Interval
FR	Fixed Ratio
IRT	Inter Response Time
L-E	Long Evans
N/A	Not Applicable
NaAc	sodium acetate
Pb	lead-exposed group
$Pb(Ac)_2$	lead acetate
PbB	blood lead
PND	Post-Natal Day
S	Subject
S-D	Sprague Dawley
TO	Time Out
U/l	µmol ALAD/min x liter erythrocytes
VI	Variable Interval
W	Wistar
WGTA	Wisconsin General Testing Apparatus
X	experimental group

TABLE 12-4. RECENT ANIMAL TOXICOLOGY STUDIES OF LEAD EFFECTS ON LEARNING IN PRIMATES

Reference	Experimental animal (species or strain)	Lead exposure: Pb conc. (medium)	Lead exposure: period (route)	Treatment groups (n)	Litters per group	Tissue lead (age measured)	Age at testing	Testing paradigm (task)	Non-behavioral effects	Behavioral results
Bushnell & Bowman (1979a) Expt. 1	Monkey (Macaca mulatta)	~0.07 or 0.16% (milk) adjusted to maintain target PbB	Daily for 1st yr (direct)	C (4) Pb_1 (3) Pb_2 (3)	N/A	PbB (1st yr): C: ~5 µg/dl* Pb_1: 37* Pb_2: 58*	5-10 mo	WGTA (form discrim. reversal learning)	None	Both Pb-exposed groups retarded in reversal learning; Pb_2-Ss especially impaired on 1st reversal following overtraining.
Expt. 2 Test 1		--same as Expt. 1--		C (4) Pb_1 (4) Pb_2 (4)	N/A	PbB (1st yr): C: ~4 µg/dl* Pb_1: 32* Pb_2: 65*	1.5-4.5 mo	2-choice maze (discr. reversal learning) non-food reward	None	Pb_2-Ss sig. retarded on 1st reversal (confirms Expt. 1 using different task and reward to control for possible confounding by motivational or motor factors).
Test 2		----------Continuation of Expt. 2----------					5-12 mo	WGTA (series of 4 reversal discr. problems)	None	Both Pb groups retarded in reversal learning; Pb_2-Ss impaired on 1st reversals regardless of prior overtraining.
Test 3		---------Continuation of Expt. 2--------- after exposure terminated at 12 mo				PbB (16 mo): C: ~5 µg/dl Pb_1: 19 Pb_2: 46	15 mo	WGTA (discr. reversal learning, more	None	Pb_2-Ss retarded on 1st reversal.
Bushnell & Bowman (1979b)	Monkey (Macaca mulatta)	--Continuation of Bushnell & Bowman (1979a)--				PbB (56 mo): C: 4 µg/dl Pb_1: 5 Pb_2: 6	49-55 mo	WGTA (spatial discr. reversal learning)	None	Both Pb-exposed groups retarded in reversal learning; 3 Pb_2-Ss failed to retain motor pattern for operating WGTA from 2 yrs earlier.

*Corrected annual averages obtained from Bushnell (1978)

TABLE 12-4 (continued)

Reference	Experimental animal (species or strain)	Lead exposure: Pb conc. (medium)	Lead exposure: period (route)	Treatment groups (n)	Litters per group	Tissue lead (age measured)	Age at testing	Testing paradigm (task)	Non-behavioral effects	Behavioral results
Rice & Willes (1979)	Monkey (Macaca fascicularis)	500 µg/kg (milk)	Daily for 1st year (direct)	C (4) Pb (4)	N/A	PbB (200 d): C: <5 µg/dl Pb: 35-70 (400 d): Pb: 20-50	421-714 d	WGTA (form discrim. reversal)	None	Pb-Ss slower to learn successive reversals.
Rice et al. (1979)	----------Continuation of Rice & Willes (1979)----------					PbB (400+ d): 20-30 µg/dl	2.5-3 yr	Operant (mult. FI-TO)	None	Pb-Ss responded at higher rates, had shorter IRTs, and tended to respond more during time-out (unrewarded).

Abbreviations:

?	information not given in report	NaAc	sodium acetate
ALA-D	delta Aminolevulinic Acid Dehydrase	Pb	lead-exposed group
C	Control group	$Pb(Ac)_2$	lead acetate
CD	substrain of Sprague Dawley	PbB	blood lead
DRH	Differential Reinforcement of High response rates	PND	Post-Natal Day
F_1	1st Filial generation	S	Subject
F_2	2nd Filial generation	S-D	Sprague Dawley
FI	Fixed Interval	TO	Time Out
FR	Fixed Ratio	U/l	µmol ALAO/min x liter erythrocytes
IRT	Inter Response Time	VI	Variable Interval
L-E	Long Evans	W	Wistar
N/A	Not Applicable	WGTA	Wisconsin General Testing Apparatus
		X	experimental group

learning task performances by rats with blood lead levels below 30 µg/dl. Winneke et al. (1977) exposed Wistar rats in utero and postnatally to a diet containing 0.07 percent lead as lead acetate. Between PND 100 and 200 the subjects were tested on two types of visual discrimination learning tasks using either "easy" stimuli (vertical vs. horizontal stripes) or "difficult" stimuli (white circles or differing diameters). Blood lead concentrations were measured at about PND 16 (26.6 µg/dl) and PND 190 (28.5 µg/dl). Although there were no significant differences between lead-exposed and control subjects on the easy discrimination task, the lead-exposed subjects performed significantly ($p < 0.01$) worse than controls on the size discrimination task. The performance of the lead group continued around change level (50 percent correct) essentially throughout the 4-week training period; control subjects began to improve after about 2 weeks of training and reached an error rate of about 15 percent by 3 to 4 weeks. Stated differently, 8 out of 10 control animals reached criterion performance levels within 27 days, whereas only one of the lead-exposed subjects did ($p < 0.01$).

More recently, Winneke et al. (1982c) repeated the size discrimination experiment and added another test involving shock avoidance. As in the earlier study, exposure started in utero and continued through behavioral testing. Different concentrations of lead acetate in the diet were used to yield average blood lead levels of 18.3 and 31.2 µg/dl after 130 days of feeding, compared to 5 µg/dl for control subjects. These values were not determined directly from the subjects in this study but were based on separate work by Schlipköter and Winneke (1980). However, ALA-D activity was measured directly in selected female subjects at PND-90 and was found to be inhibited 73 percent and 83 percent, respectively, for the different levels of lead exposure. Consistent with their earlier findings, Winneke et al. (1982c) found that lead-exposed subjects were significantly slower to reach criterion performance levels on the size discrimination task. However, on the shock avoidance task, the lead-exposed subjects were significantly quicker than control subjects to reach the criterion of successful performance. Although seemingly incongruous with the impairment found in the discrimination task, the latter finding is consistent with results obtained by Driscoll and Stegner (1976), who found performance on a shock avoidance task enhanced by lead exposure at a level high enough (~0.15 percent lead in dams' drinking water) to cause a 20 percent weight reduction in the subjects prior to weaning. Both the size discrimination deficits and the enhanced avoidance performance are indicative of alterations in normal neural functioning consequent to lead exposure.

Cory-Slechta and Thompson (1979) exposed Sprague-Dawley rats to 0.0025, 0.015, or 0.05 percent drinking water solutions of lead as lead acetate starting at PND 20-22. Operant conditioning on a fixed-interval 30-second schedule of reinforcement (food pellet delivered upon the first bar-press occurring at least 30 sec after preceding pellet delivery) began at PND

55-60. Blood lead concentrations measured at approximately PND 150 were reported in graphical form roughly as follows: 0.0025-percent solution group, 5 to 10 µg/dl PbB; 0.015-percent group, 25 to 30 µg/dl PbB; 0.05-percent group, 40 to 45 µg/dl PbB. Subjects exposed to 0.0025 or 0.015 percent lead solutions showed a "significantly" (no probability value reported) higher median response rate than matched controls during the first 30 sessions of training; response rates continued to be significantly higher over the next 60 sessions for the 0.0025-percent group and over the next 30 sessions for the 0.015-percent group (at which points training terminated for each group). Moreover, latencies to the first response in the 30-sec interval (the beginning of the typical "fixed-interval scallop" cumulative response pattern) were significantly shorter in the 0.0025- and 0.015-percent groups. However, response rates for the group exposed to the 0.05 percent solution were significantly lower than the control group's rates for the first 40 sessions; correspondingly, response latencies were longer for the highest exposure group.

Other work by Cory-Slechta et al. (1981) repeated the earlier study's exposure regimen (using 0.005 and 0.015 percent solutions) and examined the effects on another aspect of operant performance. In this study the subjects were required to depress a bar for a specified minimum duration (0.5 to 3.0 sec) before a food pellet could be delivered. Intersubject variability increased greatly in the lead-exposed groups (see also, e.g., Cory-Slechta and Thompson, 1979; Dietz et al., 1978; Hastings et al., 1979). In general, though, treated subjects tended to shorten their response durations ($p = 0.04$ for the 0.005-percent group; $p = 0.03$ for the 0.015-percent group). This tendency would contribute toward a reduced rate of reinforcement, which is associated with (and perhaps accounts for) an observed tendency toward increased response latencies in the lead-exposed subjects ($p = 0.04$ in the 0.015-percent group). Although blood lead values were not reported by Cory-Slechta et al. (1981), brain lead concentrations at approximately PND 200 ranged from 40 to 142 ng/g for the 0.005-percent group and 320 to 1080 ng/g for the 0.015-percent group. Given the same exposure regimens in the two studies, blood lead values should be comparable.

The Gross-Selbeck and Gross-Selbeck (1981) study (partly described below in Section 12.4.3.1.5) also tested Wistar rats exposed post-weaning to a diet containing 0.05 percent lead daily until completion of behavioral testing at ~180 days of age, at which time the average blood lead level was 22.7 µg/dl. Although no differences were apparent in preliminary operant barpress training, differences between lead-treated and control groups did appear when the subjects were required to bar-press at a very high rate (e.g., 2 presses per second). The lead-treated subjects outperformed, i.e., bar-pressed more rapidly than, the control subjects.

Except for monkeys, few other species have recently been studied in sufficient detail to warrant discussion here. One of the primate studies, that by Bushnell and Bowman (1979b),

is discussed under Section 12.4.3.1.5 because it examined learning ability some time after neonatal exposure to lead had terminated. In brief, that study showed impaired discrimination reversal learning performance at 40 months of age, even though lead exposure was limited to the first 12 months and the mean blood lead level was about 32 µg/dl for the "low-lead" group during that period. When measured following behavioral testing, average blood lead concentrations were similar to control levels, i.e., 5-6 µg/dl.

Other studies of nonhuman primates, however, have examined learning ability while lead exposure was ongoing. In a more comprehensive report, to which the above-described study (Bushnell and Bowman, 1979b) was a follow-up, Bushnell and Bowman (1979a) ran a series of tests on discrimination reversal learning in rhesus monkeys over the second through sixteenth months of life. Lead acetate was fed to the subjects during the first 12 months so as to maintain nominal blood lead levels of 50 and 80 µg/dl in the low-lead and high-lead groups (actual blood lead concentrations varied considerably during the first year, particularly for the high-lead groups). Although lead dosing was terminated at 12 months, blood lead levels were still somewhat elevated over control levels at the completion of behavioral testing (18.75 ± 2.87 µg/dl, low-lead group; 46.25 ± 6.74 µg/dl, high-lead group). The basic finding that appeared consistently throughout this series of tests, including two separate experiments involving different groups of subjects (see Table 12-4), was that young rhesus monkeys with blood lead levels on the order of 30 to 50 µg/dl, compared to control groups with levels of approximately 5 µg/dl, were significantly retarded in their ability to learn a visual discrimination task in which the cues were reversed from time to time according to specified criteria. In addition, the higher exposure subjects were especially slow in mastering the first reversal problem, following extended training on the original discrimination task.

Rice and Willes (1979) attempted to replicate the Bushnell and Bowman (1979a) findings. They fed Rhesus monkeys lead acetate from day one of life and obtained blood lead concentrations in their four experimental subjects between 35 and 70 µg/dl around PND 200, which dropped to 20-50 µg/dl by PND 400; the four control subjects' levels were generally 5 µg/dl or lower. At 2-3 years of age, while lead exposure continued, the subjects were trained on a WGTA form-discrimination task similar to that used by Bushnell and Bowman (1979a). Consistent with the latter study, Rice and Willes (1979) used a reversal-learning paradigm in which the correct discriminative cue was reversed once the task was mastered. Although initially the lead-treated monkeys performed better than controls (fewer trials to criterion and fewer errors), over successive reversals (4 through 12) the control subjects made fewer errors and required fewer trials to reach criterion performance in each daily session. This difference disappeared following session 12, which was extended 500 trials beyond the criterion level ("overtraining"). Overall, the lead-treated subjects appeared to make more errors in per-

forming the reversal tasks; analysis of variance yielded a significant main effect ($p = 0.05$), but this applied only to sessions 6 through 12, which would seem to be a somewhat arbitrary selection of data for analysis. The authors did note, however, that the success of the lead-treated monkeys in the first few trials appeared to result from the treated subjects' reluctance to manipulate the novel negative stimulus after 100 pretraining trials in which only the positive stimulus was presented. Thus, the unexpected initial success of the lead-exposed subjects may have been an artifact of the pretraining procedure. By this interpretation, the lead-treated monkeys in Rice and Willes' (1979) study and the high-lead group of monkeys in Bushnell and Bowman's (1979a) study were both showing perturbed behavior, that is, refractoriness to alter their behavior under changed conditions.

Rice and her coworkers studied the same two groups of subjects at 2-3 years of age on an operant conditioning task involving a multiple fixed-interval/time-out schedule of reinforcement (Rice et al., 1979). This schedule alternated a 10- to 90-sec time-out period, during which responses were unrewarded, with an 8-min fixed interval, at the end of which a push on a lighted disk was rewarded. The lead-treated monkeys, whose blood-lead levels had by then stabilized at 20-30 µg/dl, showed a higher response rate than controls during the fixed interval and shorter pauses between responses (lower median interresponse times). The treated monkeys also tended to respond more during the time-out period, even though responses were not rewarded.

In conclusion, it appears that alterations in behavior in rats and monkeys occur as a consequence of chronic exposure to dietary lead resulting in blood lead levels on the order of 30-50 µg/dl. These alterations in behavior are clearly indicative of altered neural functioning, especially in the CNS in view of certain of the tasks employed. Another question that arises, however, is whether such alterations represent impairment in overall functioning of the lead-exposed subjects. As some studies indicate, lead-treated subjects may actually perform better than non-treated control subjects on certain learned tasks. For example, in the Winneke et al. (1982c) study, the task on which lead-exposed rats excelled required the subjects to move from one compartment to the other in a two-compartment shuttle box in order to avoid receiving an electrical shock to the feet. A successful avoidance response had to occur within 5 seconds after the onset of a warning stimulus. Similar findings have been reported by Driscoll and Stegner (1976) for shock-avoidance performance. As previously described, a study by Gross-Selbeck and Gross-Selbeck (1981) required rats to press a bar for food under an operant conditioning schedule that rewarded only high rates of responding. By responding more rapidly, the lead-treated subjects were more successful than untreated control subjects in maximizing their rewards.

Because of the contingencies of reinforcement specified in the just-cited experiments, a tendency to respond with greater alacrity or less hesitation was properly adaptive for the subjects. Other conditions, however, could make the same tendency unadaptive, as, for example, in the study by Cory-Slechta et al. (1981), which required rats to press a bar and hold it down longer than rats are normally inclined to do. In that case the lead-treated subjects were less successful than untreated controls. Thus, success or failure (or enhancement or impairment of performance) may be misleading designations for the behavioral alterations measured under arbitrary experimental conditions (cf. Penzien et al., 1982). Of greater importance may be the underlying tendency to respond more rapidly or "excessively," regardless of whether or not such responding is appropriate for the reinforcement contingencies of an experiment. Such a tendency may be inferred from results of other studies of the neurotoxic effects of lead (e.g., Angell and Weiss, 1982; Overmann, 1977; Rice et al., 1979). Taken together, these reports might be interpreted as suggesting a possible "hyper-reactivity" (cf. Winneke et al., 1982c) in lead-treated animals. They and others (e.g., Petit and Alfano, 1979) have noted the commonality of such types of behavioral deficits with experimental studies of lesions to the hippocampus (see also Sections 12.4.3.2.1 and 12.4.3.5.).

12.4.3.1.4 Effects of lead on social behavior. The social behavior and organization of even phylogenetically closely related species may be widely divergent. For this and other reasons, there is little or no basis to assume that, for example, aggressiveness in a lead-treated Rhesus monkey provides a model of aggressiveness in a lead-exposed human child. However, there are other compelling grounds for including animal social behavior in the present review. As in the case of nonsocial behavior patterns, characteristics of an animal's interactions with conspecifics may reflect neurological (especially CNS) impairment due to toxic exposure. Also, certain aspects of animal social behavior have evolved for the very purpose (in a nonteleological sense) of indicating an individual's physiological state or condition (Davis, 1982). Such behavior could potentially provide a sensitive and convenient indicator of toxicological impairment.

Two early reports (Silbergeld and Goldberg, 1973; Sauerhoff and Michaelson, 1973) suggested that lead exposure produced increased aggressiveness in rodents. Neither report, however, attempted to quantify these observations of increased aggression. Later, Hastings et al. (1977) examined aggressive behavior in rats that had been exposed to lead via their dams' milk. Solutions containing 0, 0.01, or 0.05 percent lead as lead acetate constituted the dams' drinking water from parturition to weaning at PND 21, at which time exposure was terminated. This lead treatment produced no change in growth of the pups. Individual pairs of male offspring (from the same treatment groups) were tested at PND 60 for shock-elicited aggression. Both lead-exposed groups (average blood lead levels of 5 and 9 µg/dl and brain lead levels of

8 and 14 µg/100g) showed significantly less aggressive behavior than the control group. There were no significant differences among the groups in the flinch/jump thresholds to shock, which suggests that the differences seen in shock-elicited aggression were not caused by differences in sensitivity to shock.

A study by Drew et al. (1979) utilized apomorphine to induce aggressive behavior in 90-day-old rats and found that earlier lead exposure attenuated the drug-induced aggressiveness. Lead exposure occurred between birth and weaning primarily through the dams' milk or through food containing 0.05 percent lead as lead acetate. No blood or tissue concentrations of lead were measured. There were no significant differences in the weights of the lead-treated and control animals at PND 10, 20, 30, or 90.

Using laboratory mice exposed as adults, Ogilvie and Martin (1982) also observed reduced levels of aggressive behavior. Since the same subjects showed no differences in vitality or open field activity measures, the reduction in aggressiveness did not appear to be due to a general effect of lead on motor activity. Blood lead levels were estimated from similarly treated groups as being approximately 160 µg/dl after 2 weeks of exposure and as 101 µg/dl after 4 weeks of exposure.

Cutler (1977) used ethological methods to assess the effects of lead exposure on social behavior in laboratory mice. Subjects were exposed from birth (via their dams' milk) and post-weaning to a 0.05 percent solution of lead as lead acetate (average brain lead concentrations were 2.45 nmol/g for controls and 4.38 nmol/g for experimental subjects). At 8 weeks of age social encounters between subjects from the same treatment group were analyzed in terms of numerous specified, identifiable behavioral and postural elements. The frequency and duration of certain social and sexual investigative behavior patterns were significantly lower in lead-treated mice of both sexes than in controls. Lead-exposed males also showed significantly reduced agonistic behavior compared with controls. Overall activity levels (nonsocial as well as social behavior) were not affected by the lead treatment. Average body weights did not differ for the experimental and control subjects at weaning or at the time of testing.

A more recent study by Cutler and coworkers (Donald et al., 1981) used a similar paradigm of exposure and behavioral evaluation, except that exposure occurred either only prenatally or postnatally and testing occurred at two times, 3-4 and 14-16 weeks of age. Statistically significant effects were found only for the postnatal exposure group. Although total activity in postnatally exposed mice did not differ from that of controls at either age of testing, the incidence of various social activities did differ significantly. As juveniles (3-4 weeks old), lead-treated males (and to some extent, females) showed decreased social investigation of a same-sex conspecific. This finding seems to be consistent with Cutler's (1977) earlier observations made at 8 weeks of age. Aggressive behavior, however, was almost

nonexistent in both control and lead-treated subjects in the later study, and so could not be compared meaningfully. Although the authors do not comment on this aspect of their study, it seems likely that differences in the strains of laboratory mice used as subjects could well have been responsible for the lack of aggressive behavior in the Donald et al.'s (1981) study (cf., e.g., Adams and Boice, 1981). Later testing at 14 to 16 weeks revealed that lead-exposed female subjects engaged in significantly more investigative behavior of a social or sexual nature than did control subjects, while males still showed significant reductions in such behavior when encountering another mouse of the same sex. This apparent disparity between male and female mice is one of relatively few reports of gender differences in sensitivity to lead's effects on the nervous system (cf. Cutler, 1977; Verlangieri, 1979). In this case, Donald et al. (1981) hypothesized that the disparity might have been due to differences in brain lead concentrations: 74.7 μmol/kg in males versus 191.6 μmol/kg in females (blood lead concentrations were not measured). The Donald et al. (1981) study, along with the above-mentioned study of Ogilvie and Martin (1982), point out the importance of not focusing exclusively on perinatal exposure in assessing neurotoxic effects of chronic lead exposure.

The social behavior of rhesus monkeys has also been evaluated as a function of early lead exposure. A study by Allen et al. (1974) reported persistent perturbations in various aspects of the social behavior of lead-exposed infant and juvenile monkeys, including increased clinging, reduced social interaction, and increased vocalization. However, exposure conditions varied considerably in the course of this study, with overt toxicity being evident as blood lead levels at times ranged higher than 500 μg/dl.

A more recent study consisting of four experiments (Bushnell and Bowman, 1979c) also examined social behavior in infant Rhesus monkeys, but under more systematically varied exposure conditions. In experiments 1 and 2, daily ingestion of lead acetate during the first year of life resulted in blood lead levels of 30-100 μg/dl, with consequent suppression of play activity, increased clinging, and greater disruption of social behavior when the play environment was altered. Experiment 3, a comparison of chronic and acute lead exposure (the latter resulting in a peak blood lead concentration of 250-300 μg/dl during weeks 6-7 of life), revealed little effect of acute exposure except in the disruption that occurred when the play environment was altered. Otherwise, only the chronically exposed subjects differed significantly from controls in various categories of social behavior. Experiment 4 of the study showed that prenatal exposure alone, with blood lead concentrations of exposed infants ranging between 33 and 98 μg/dl at birth, produced no detectable behavioral effects under the same procedures of evaluation. Overall, neither aggressiveness nor dominance was clearly affected by lead exposure.

Another aspect of social behavior--interaction between mothers and their offspring--was examined in lead-exposed rats by Zenick et al. (1979). Dams chronically received up to 400 mg/kg lead acetate in their drinking water on a restricted daily schedule (blood lead concentrations averaged 96.14 ± 16.54 µg/dl in the high-exposure group at day 1 of gestation). Dams and their litters were videotaped on PND 1-11, and the occurrence of certain behavior patterns (e.g., lying with majority of pups, lying away from pups, feeding) was tabulated by the experimenters. In addition, dams were tested for their propensity to retrieve pups removed from the nest. Neither analysis revealed significant effects of lead exposure on the behavior of the dams. However, restricted access to drinking water (whether lead-treated or not) appeared to confound the measures of maternal behavior.

The above studies suggest that aggressive behavior in particular is, if anything, reduced in laboratory animals as a result of exposure to lead. Certain other aspects of social behavior in laboratory mice, namely components of sexual interaction and social investigation, also appear to be reduced in lead-treated subjects, although there may be gender differences in this regard following chronic post-maturational exposure. Young rhesus monkeys also appear to be sensitive to the disruptive effects of lead on various aspects of social behavior. All of these alterations in social behavior are indicative of altered neural functioning as a consequence of lead exposure in several mammalian species.

12.4.3.1.5 Persistence of neonatal exposure effects. The specific question of persisting, long-term consequences of lead effects on the developing organism has been addressed in a number of studies by carrying out behavioral testing some time after the termination of lead exposure. Such evidence of long-term effects has been reported for rhesus monkeys by Bushnell and Bowman (1979b). Their subjects were fed lead acetate so as to maintain blood lead (PbB) levels of either 50 ± 10 (low-lead) or 80 ± 10 µg/dl (high-lead) throughout the first year of life (actual means and standard errors for the year were reported as 31.71 ± 2.75 and 65.17 ± 6.28 µg/dl). Lead treatment was terminated at 12 months of age, after which blood lead levels declined to around 5 - 6 µg/dl at 56 months. At 49 months of age the subjects were reintroduced to a discrimination reversal training procedure using new discriminative stimuli. Despite their extensive experience with the apparatus (Wisconsin General Test Apparatus) during the first two years of life, most of the high-lead subjects failed to retain the simple motor pattern (pushing aside a small wooden block) required to operate the apparatus. Remedial training largely corrected this deficit. However, both high- and low-lead groups required significantly more trials than the control group ($p < 0.05$) to reach criterion performance levels. This difference was found only on the first discrimination task and nine reversals of it. Successive discrimination problems showed no differential performance effects, which indicates that with continued training the lead-treated subjects were able to achieve the same level of performance as controls.

Studies using rats have also suggested that behavioral perturbations may be evident some time after the termination of exposure to lead. Hastings et al. (1979) exposed rat pups to lead through their mothers' milk by providing the dams 0.01 or 0.1 percent solutions of lead as lead acetate for drinking water. Exposure was stopped at weaning, at which time average blood-lead values were 29 (± 5) and 65 (± 25) µg/dl, respectively. At 120 days of age the subjects were placed on an operant conditioning simultaneous visual discrimination task. Although Hastings et al. (1979) did not actually measure blood lead levels in adult subjects at the time of behavioral testing, they presumed that the levels for control and experimental groups were by then probably quite similar, i.e., on the order of 10 µg/dl, based on prior work (Hastings et al., 1977.) Forty-six percent of the high-lead group and 37 percent of the low-lead group failed to learn the task within 60 days; only 4 percent of the control group failed to reach criterion. In terms of time to reach criterion, controls required a mean of 23 days while the low-lead subjects required 32 days and the high-lead rats 39 days (high-lead vs. controls, $p < 0.01$). Additional testing on a successive discrimination task at 270 days of age and a go/no-go discrimination task at 330 days revealed no significant differences between controls and lead-treated subjects. Since the three tests were not counter-balanced in presentation, there is no way to determine whether the lack of effects in the two latter tests may have been a function of the order of testing or age at the time of testing or, more simply, a function of the latter tests' lack of sensitivity to neurotoxic effects.

Gross-Selbeck and Gross-Selbeck (1981) also found alterations in the operant behavior of adult rats after perinatal exposure to lead via mothers whose blood lead levels averaged 20.5 µg/dl. At the time of testing (3 to 4 months postnatally) the lead-exposed subjects' blood lead levels averaged 4.55 µg/dl, compared to 3.68 µg/dl in control subjects. Although the two groups appeared qualitatively similar in their behavior in an open-field test and in preliminary bar-press training, the lead-exposed subjects tended to respond at a much higher rate than did control subjects when rewarded for responding quickly. Since the schedule differentially reinforced high response rates, the lead-exposed subjects performed more successfully than did the control subjects. This was true for three different variations on the basic schedule examined by the authors. As noted earlier, in this case, the heigtened response rate was adaptive within the context of the particular task used but may not have been under other contingencies. Most importantly here, it is indicative of altered CNS function persisting for months beyond the cessation of lead exposure early in development.

Results from the above studies indicate that behavioral effects may exist as sequelae to past lead exposure early in development of mammalian species, even though blood lead levels at the time of later behavioral assessment are essentially "normal."

12.4.3.2 Morphological Effects

12.4.3.2.1 In vivo studies. Recent key findings on the morphological effects of in vivo lead exposure on the nervous system are summarized in Table 12-5. It would appear that certain types of glial cells are sensitive to lead exposure, as Reyners et al. (1979) found a decreased density of oligodendrocytes in cerebral cortex of young rats exposed from birth to 0.1 percent lead in their food. Higher exposure concentrations (0.2-0.4 percent lead salts), especially during the prenatal period (Bull et al., 1983), can reduce synaptogenesis and retard dendritic development in the cerebral cortex (McCauley and Bull, 1978; McCauley et al., 1979, 1982) and the hippocampus of developing rats (Campbell et al., 1982, and Alfano and Petit, 1982). Some of these effects, e.g. on cerebral cortex appear to be transient (McCauley et al., 1979, 1982). Suckling rats subjected to increasing exposures of lead exhibit more pronounced effects, such as reduction in the number and average diameter of axons in the optic nerve at 0.5 percent lead acetate exposure (Tennekoon et al., 1979), a general retardation of cortical synaptogenesis at 1.0 percent lead carbonate exposure (Averill and Needleman, 1980), or a reduction in cortical thickness at 4.0 percent lead carbonate exposure (Petit and LeBoutillier, 1979). This latter exposure concentration also causes a delay in the onset and peak of Schwann cell division and axonal regrowth in regenerating peripheral nerves in chronically exposed adult rats (Ohnishi and Dyck, 1981). In short, both neuronal and glial components of the nervous system appear to be affected by neonatal or chronic lead exposure.

Organolead compounds have also been demonstrated to have a deleterious effect on the morphological development of the nervous system. Seawright et al. (1980) administered triethyl lead acetate (Et_3Pb) by gavage to weanling (40-50 g) and "young adult" (120-150 g) rats. Single doses of 20 mg Et_3Pb/kg caused impaired balance, convulsions, paralysis, and coma in both groups of treated animals. Peak levels in blood and brain were noted two days after exposure, with extensive neuronal necrosis evident in several brain regions by three days post-treatment. Weekly exposures to 10 mg Et_3Pb/kg for 19 weeks resulted in less severe overt signs of intoxication (from which the animals recovered) and moderate to severe loss of neurons in the hippocampal region only.

12.4.3.2.2 In vitro studies. Björklund et al. (1980) placed tissue grafts of developing nervous tissue in the anterior eye chambers of adult rats. When the host animals were given 1 or 2 percent lead acetate in their drinking water, the growths of substantia nigral and hippocampal, but not cerebellar, grafts were retarded. Grafts of the developing cerebral cortex in host animals receiving 2 percent lead exhibited a permanent 50 percent reduction in size (volume), whereas 1 percent lead produced a slight increase in size in this tissue type. The authors felt that this anomalous result might be explained by a hyperplasia of one particular cell type at lower concentrations of lead exposure.

TABLE 12-5. SUMMARY OF KEY STUDIES OF MORPHOLOGICAL EFFECTS OF IN VIVO LEAD EXPOSURE

Species	Exposure protocol	Peak blood lead level	Observed effect	Reference
Young rats	0.1% Pb^{++} in chow PND 0-90		Decreased density of oligodendrocytes in cerebral cortex	Reyners et al. (1979)
	0.1% $Pb(Ac)_2$ in dams' drinking water PND 0-32		Significant inhibition in myelin deposition and maturation in whole brain	Stephens and Gerber (1981)
	0.2% $PbCl_2$ in dams' drinking water from gestation thru PND0	80 µg/dl at birth	Less mature synoptic profile in cerebral cortex at PND-15	McCauley and Bull (1978) McCauley et al. (1979)
			30% reduction in synoptic density in cerebral cortex at PND15 (returned to normal at PND21)	McCauley et al. (1982)
	0.2% $Pb(Ac)_2$ in dams' drinking water PND 0-25		15-30% reduction in synaptic profiles in hippocampus	Campbell et al. (1982)
	0.4% $PbCO_3$ in dams' drinking water PND 0-30		Retardation in temporal sequence of hippocampal dendritic development	Alfano and Petit (1982)
	0.5% $Pb(Ac)_2$ in dams' drinking water PND 0-21		10-15% reduction in number of axons in optic nerve; skewing of fiber diameters to smaller sizes	Tennekoon et al. (1979)
	1% $PbCO_3$ in chow PND 0-60	385 µg/dl (PND 21)	Retardation of cortical synaptogenesis over and above any nutritional effects	Averill and Needleman (1980)
	4% $PbCO_3$ in dams' chow PND 0-28	258 µg/dl (PND 28)	13% reduction in cortical thickness and total brain weight; reduction in synaptic density	Petit and LeBoutillier (1979)
	4% $PbCO_3$ in dams' chow PND 0-25		Reduction in hippocampal length and width; similar reduction in afferent projection to hippocampus	Alfano et al. (1982)
Adult rats	4% $PbCO_3$ in chow for 3 mos.		Delay in onset and peak of Schwann cell division and axonal regrowth in regenerating nerves	Ohnishi and Dyck (1981)
	4% $PbCO_3$ in chow PND 0-150	300 µg/dl (PND 150)	Demyelination of peripheral nerves beginning PND 20-35	Windebank et al. 1980

PND: post-natal day

$Pb(Ac)_2$: lead acetate

$PbCO_3$: lead carbonate

Organolead compounds have also been demonstrated to affect neuronal growth (Grundt et al., 1981). Cultured cells from embryonic chick brain were exposed to 3.16 μM triethyllead chloride in the incubation medium for 48 hr, resulting in a 50 percent reduction in the number of cells exhibiting processes. There was no observed effect on glial morphology.

Other investigations have focused on morphological aspects of the blood-brain barrier and its possible disruption by lead intoxication (Kolber et al., 1980). Capillary endothelial cells isolated from rat cerebral cortex and exposed to 100 μM lead acetate in vitro (Silbergeld et al., 1980b) were examined by electron microscopy and X-ray microprobe analysis. Lead deposits were found to be sequestered preferentially in the mitochondria of these cells in much the same manner as calcium. This affinity may be the basis for lead-induced disruption of transepithelial transport of Ca^{2+} and other ions.

12.4.3.3 Electrophysiological Effects.

12.4.3.3.1 In vivo studies. Recent key findings on the electrophysiological effects of in vivo lead exposure are summarized below in Table 12-6. The visual system appears to be particularly susceptible to perturbation by neonatal lead exposure. Suckling rats whose dams were given drinking water containing 0.2 percent lead acetate had significant alterations in their visual evoked responses (VER) and decreased visual acuity at PND 21, at which time their blood lead levels were 65 μg/dl (Cooper et al., 1980; Fox et al., 1977; Impelman et al., 1982; Fox and Wright, 1982; Winneke, 1980). Both of these observations are indicative of depressed conduction velocities in the visual pathways. These same exposure levels also increased the severity of the maximal electroshock seizure (MES) response in weanling rats who exhibited blood lead levels of 90 μg/dl (Fox et al., 1978, 1979). The authors speculated that neonatal lead exposure acts to increase the ratio of excitatory to inhibitory systems in the developing cerebrospinal axis. Such exposure can also lead to lasting effects on the adult nervous system, as indicated by persistent decreases in visual acuity and spatial resolution in 90-day old rats exposed only from birth to weaning to 0.2 percent lead acetate (Fox et al., 1982).

The adult nervous system is also vulnerable to lead-induced perturbation at low levels of exposure. Hietanen et al. (1980) found that chronic exposure of adult rabbits to 0.2 percent lead acetate in drinking water resulted in an 85 percent inhibition of motor conduction velocity in the sciatic nerve.

12.4.3.3.2 In vitro studies. Palmer et al. (1981) and Olson et al. (1981) looked at intraocular grafts of cerebellar tissue from 14- to 15-day-old rats in host animals treated for 2 months with drinking water containing 1 percent lead acetate, followed by plain water for 4-5 months. They found no alterations in total growth or morphology of grafts in treated vs. control hosts, yet the Purkinje neurons in the lead-exposed grafts had almost no spontaneous activity. Host cerebellar neurons, on the other hand, and both host and graft neurons in

TABLE 12-6. SUMMARY OF KEY STUDIES OF ELECTROPHYSIOLOGICAL EFFECTS OF IN VIVO LEAD EXPOSURE

Species	Exposure protocol	Peak blood lead level	Observed effect	Reference
Suckling rat	0.2% $Pb(Ac)_2$ in dams' drinking water PND 0-20	90 µg/dl (PND 20)	More rapid appearance and increased severity of MES response	Fox et al. (1978, 1979)
	0.2% $Pb(Ac)_2$ in dams' drinking water PND 0-21	65 µg/dl (PND 21)	1) Increased latencies and decreased amplitudes of primary and secondary components of VER; 2) decreased conduction velocities in visual pathways; 3) 25-50% decrease in scotopic visual acuity 4) persistent decreases in visual acuity and spatial resolution at PND 90	Fox et al. (1977); Impelman et al. (1982); Cooper et al. (1980); Winneke (1980); Fox and Wright (1982) Fox et al. (1982)
Young rhesus monkeys	$Pb(Ac)_2$ solutions in food PND 0-365	300 µg/dl (PND 60) 85 µg/dl	Severe impairment of discrimination accuracy; loss of scotopic function	Bushnell et al. (1977)
Adult rabbit	0.2% $Pb(Ac)_2$ in drinking water for 4 weeks		85% reduction in motor conduction velocity of sciatic nerve	Hietanen et al. (1980)

PND: post-natal day
$Pb(Ac)_2$: lead acetate
MES: maximal electroshock seizure
VER: visual evoked response

control animals, all exhibited significant levels of spontaneous activity. Taylor et al. (1978) recorded extracellularly from cerebellar Purkinje cells in adult rats both in situ and in intraocular grafts in an effort to determine what effect lead had on the norepinephrine (NE)-induced inhibition of Purkinje cell spontaneous discharge. Application of exogenous NE to both in situ and in oculo cerebellum produced 61 and 49 percent inhibitions of spontaneous activity, respectively. The presence of 5-10 μM lead reduced this inhibition to 28 and 13 percent, respectively. This "disinhibition" was specific for NE, as responses to both cholinergic and parallel fiber stimulation in the same tissue remained the same. Furthermore, application of lead itself did not affect spontaneous activity, but did inhibit adenylate cyclase activity in cerebellar homogenates at the same concentration required to disinhibit the NE-induced reduction of spontaneous activity (3 to 5 μM).

Fox and Sillman (1979) looked at receptor potentials in the isolated, perfused bullfrog retina and found that additions of lead chloride caused a reversible, concentration-dependent depression of rod (but not cone) receptor potentials. Concentrations of 5 μM produced an average 16 percent depression, while 12.5 μM produced an average 23 percent depression.

Evidence that lead does indeed resemble other divalent cations, in that it appears to interfere with chemically mediated synaptic transmission, has been obtained in studies of peripheral nerve function. For example, lead is capable of blocking neural transmission at peripheral adrenergic synapses (Cooper and Steinberg, 1977). Measurements of the contraction force of the rabbit saphenous artery following stimulation of the sympathetic nerve endings indicated that lead blocks muscle contraction by an effect on the nerve terminals rather than by an effect on the muscle. Since the response recovered when the Ca^{2+} concentration was increased in the bathing solution, it was concluded that lead does not deplete transmitter stores in the nerve terminals, but more likely blocks NE release.

It has also been demonstrated that lead depresses synaptic transmission at the peripheral neuromuscular junction by impairing acetylcholine (ACh) release from presynaptic terminals (Kostial and Vouk, 1957; Manalis and Cooper, 1973; Cooper and Manalis, 1974). This depression of neurotransmitter release evoked by nerve stimulation is accompanied by an increase in the spontaneous release of ACh, as evidenced by the increased frequency of spontaneous miniature endplate potentials (MEPPs). Kolton and Yaari (1982) found that this increase in MEPPs in the frog nerve/muscle preparation could be induced by lead concentrations as low as 5 μM.

The effects of lead on neurotransmission within the central nervous system have also been studied. For example, Kim et al. (1980) fed adult rabbits 165 mg lead carbonate per day for five days and looked at Ca^{2+} retention in brain slices. Treated animals showed a 75 percent increase in Ca^{2+} retention time, indicating that lead inhibited the mediated efflux of Ca^{2+} from the incubated brain slice. Investigation of the in vitro effects of lead on Ca^{2+} binding

was carried out by Silbergeld and Adler (1978) on caudate synaptosomes. They determined that 50 μM lead caused an 8-fold increase in $^{45}Ca^{2+}$ binding and that in both control and lead-treated preparations the addition of ATP increased binding, while ruthenium red and Ca^{2+} decreased it. Further findings in this series of experiments demonstrated that lead inhibits the Na^{+}-stimulated loss of Ca^{2+} by mitochondria and that blockade of dopamine (DA) uptake by 5 μM benztropine reversed the lead-stimulated increase in Ca^{2+} uptake by synaptosomes. The authors concluded that lead affects the normal mechanisms of Ca^{2+} binding and uptake, perhaps by chelating with DA in order to enter the nerve terminal. By inhibiting the release of Ca^{2+} bound to mitochondria there, lead essentially causes an increase in the Ca^{2+} concentration gradient across the nerve terminal membrane. As a result, more Ca^{2+} would be expected to enter the nerve terminal during depolarization, thus effectively increasing synaptic neurotransmission at dopaminergic terminals without altering neuronal firing rates.

12.4.3.4 Biochemical Alterations. The majority of previous investigations of biochemical alterations in the nervous system following exposure to lead have focused on perturbations of various neurotransmitter systems, probably because of the documentation extant on the neurophysiological and behavioral roles played by these transmitters. Recently, however, somewhat more attention has been centered on the impact of lead exposure on energy metabolism and other cellular homeostatic mechanisms such as protein synthesis and glucose transport. A significant portion of this work has, however, been conducted in vitro.

12.4.3.4.1 In vivo studies. Recent key findings on the biochemical effects of in vivo exposure are summarized in Table 12-7. Although the majority of recent work has continued to focus on neurotransmitter function, it appears that the mechanisms of energy metabolism are also particularly vulnerable to perturbation by lead exposure. McCauley, Bull, and coworkers have demonstrated that exposure of prenatal rats to 0.02 percent lead chloride in their dams' drinking water leads to a marked reduction in cytochrome content in cerebral cortex, as well as a possible uncoupling of energy metabolism. Although the reduction in cytochrome content is transient and disappears by PND 30, it occurs at blood lead levels as low as 36 μg/dl (McCauley and Bull, 1978; Bull et al., 1979); delays in the development of energy metabolism may be seen as late as PND 50 (Bull, 1983).

There does not appear to be a selective vulnerability of any particular neurotransmitter system to the effects of lead exposure. Pathways utilizing dopamine (DA), norepinephrine (NE), serotonin (5-HT), and γ-aminobutyric acid (GABA) are all affected in neonatal animals at lead-exposure concentrations of 0.2-2.0 percent lead salts in dams' drinking water. Although the blood lead values reported following exposure to the lower lead concentrations (0.2-0.25 percent lead acetate or lead chloride) range from 47 μg/dl (Goldman et al., 1980) to 87 μg/dl (Govoni et al., 1980), a few general observations can be made:

TABLE 12-7. SUMMARY OF KEY STUDIES ON BIOCHEMICAL EFFECTS OF IN VIVO LEAD EXPOSURE

Species	Exposure protocol	Peak blood lead level	Observed effect	Reference
Suckling rat	0.004% $Pb(Ac)_2$ in dams' drinking water PND 0-35		Decline in synthesis and turnover of striatal DA	Govoni et al. (1979, 1980); Memo et al. (1980a, 1981)
	0.02% $PbCl_2$ in dams' drinking water from gestation thru PND 0-21	80 µg/dl (at birth) 36 µg/dl (PND 21)	1) Transient 30% reduction in cytochrome content of cerebral cortex; 2) possible uncoupling of energy metabolism 3) delays in development of energy metabolism	McCauley and Bull (1978); McCauley et al. (1979); Bull et al. (1979) Bull (1983)
	0.2% $Pb(Ac)_2$ in dams' drinking water PND 0-21	47 µg/dl (PND 21)	1) 23% decrease in NE levels of hypotholamus and striatum; 2) increased turnover of NE in brainstem	Goldman et al. (1980)
	0.25% $Pb(Ac)_2$ in dams' drinking water PND 0-35		Decline in synthesis and turnover of striatal DA	Govoni et al. (1978a)
	0.25% $Pb(Ac)_2$ in dams' drinking water PND 0-35		Increase in DA synthesis in frontal cortex and nuc. accumbens(10-30% and 35-45%, respectively)	Govoni et al. (1979, 1980); Memo et al. (1980a, 1981)
	0.25% $Pb(Ac)_2$ in dams' drinking water PND 0-35		1) 50% increase in DA binding to striatal D_2 receptors; 2) 33% decrease in DA binding to nuc. accumbens D_2 receptors	Lucchi et al. (1981)
	0.25% $Pb(Ac)_2$ in dams' drinking water PND 0-42	87 µg/dl (PND 42)	1) 31% increase in GABA specific binding in cerebellum; 53% increase in GMP activity; 2) 36% decrease in GABA-specific binding in striatum; 47% decrease in GMP activity	Govoni et al. (1978b, 1980)

TABLE 12-7. (continued)

Species	Exposure protocol	Peak blood lead level	Observed effect	Reference
	0.25% $Pb(Ac)_2$ in dam's drinking water PND 0-21; 0.004% or 0.25% until PND 42		1) 12 and 34% elevation of GABA binding in cerebellum for 0.004% and 0.25%, respectively; 2) 20 and 45% decreases in GABA binding in striatum for 0.004% and 0.25%, respectively	Memo et al. (1980b)
	0.5-1% $Pb(Ac)_2$ in drinking water PND 0-60		1) Increased sensitivity to seizures induced by GABA blockers; 2) increase in GABA synthesis in cortex and striatum; 3) inhibition of GABA uptake and release by synaptosomes from cerebellum and basal ganglia; 4) 70% increase in GABA-specific binding in cerebellum	Silbergeld et al. (1979, 1980a)
	0.25-1% $Pb(Ac)_2$ in drinking water PND 0-60	72-91 g/dl (PND 21)	1) 40-50% reduction of whole-brain ACh by PND 21; 2) 36% reduction by PND 30 (return to normal values by PND 60)	Modak et al. (1978)
	75 mg $Pb(Ac)_2$/kg b.w./day via gastric intubation PND 2-14	98 µg/dl (PND 15)	1) 20% decline in striatal DA levels at PND 35; 2) 35% decline in striatal DA turnover by PND 35; 3) Transient depression of DA uptake at PND 15; 4) Possible decreased DA terminal density	Jason and Kellogg (1981)
Young rat	2% $Pb(Ac)_2$ in dam's drinking water PND 0-21 then 0.002-0.008% until PND 56		1) non-dose-dependent elevations of NE in midbrain (60-90%) and DA and 5-HT in midbrain, striatum and hypothalamus (15-30%); 2) non-dose-dependent depression of NE in hypothalamus and striatum (20-30%).	Dubas et al. (1978)

PND:	post-natal day	DA:	dopamine
$Pb(Ac)_2$:	lead acetate	GABA:	γ-aminobutyric acid
$PbCl_2$:	lead chloride	GMP:	guanosine monophosphate
NE:	norepinephrine	5-HT:	serotonin

(1). Synthesis and turnover of DA and NE are depressed in the striatum, and elevated in midbrain, frontal cortex, and nucleus accumbens. This seems to be paralleled by concomitant increases in DA-specific binding in striatum and decreases in DA-specific binding in nucleus accumbens, possibly involving a specific subset (D_2) of DA receptors (Lucchi et al., 1981). These findings are probably reflective of sensitization phenomena resulting from changes in the availability of neurotransmitter at the synapse.

(2). The findings for pathways utilizing GABA show similar parallels. Increases in GABA synthesis in striatum are coupled with decreases in GABA-specific binding in that region, while the converse holds true for the cerebellum. In these cases, cyclic GMP activity mirrors the apparent changes in receptor function. This increased sensitivity of cerebellar postsynaptic receptors (probably a response to the lead-induced depression of presynaptic function) is likely the basis for the finding that lead-treated animals are more susceptible to seizures induced by GABA-blocking agents such as picrotoxin or strychnine (Silbergeld et al., 1979).

12.4.3.4.2 In vitro studies. Any alterations in the integrity of the blood-brain barrier can have serious consequences for the nervous system, especially in the developing organism. Kolber et al. (1980) examined glucose transport in isolated microvessels prepared from the brains of suckling rats given 25, 100, 200, or 1000 mg lead/kg body weight daily by intragastric gavage. On PND 25, they found that even the lowest dose blocked specific transport sites for sugars and damaged the capillary endothelium. In vitro treatment of the preparation with concentrations of lead as low as 0.1 μM produced the same effects.

Purdy et al. (1981) examined the effects in rats of varying concentrations of lead acetate on the whole-brain synthesis of tetrahydrobiopterin (BH_4), a cofactor for many important enzymes, including those regulating catecholamine synthesis. Concentrations of lead as low as 0.01 μM produced a 35 percent inhibition of BH_4 synthesis, while 100 μM inhibited the BH_4 salvage enzyme, dihydropteridine reductase, by 40 percent. This would result in a decreased conversion of phenylalanine to tyrosine and thence to DOPA (the initial steps in dopamine synthesis), as well as decreases in the conversion of trytophan to its 5-hydroxy form (the initial step in serotonin synthesis). These decrements, if occurring in vivo, could not be ameliorated by increased dietary intake of BH_4, as it does not cross the blood-brain barrier.

Lead has also been found to have an inhibitory effect on mitochondrial respiration in the cerebrum and cerebellum of immature or adult rats at concentrations greater than 50 μM (Holtzman et al., 1978b). This effect, which was equivalent in both brain regions at both ages studied, is apparently due to an inhibition of nicotinamide adenine dinucleotide (NAD)-linked dehydrogenases within the mitochondrial matrix. These same authors found that this lead-induced effect, which is an energy-dependent process, could be blocked in vitro by

addition of ruthenium red to the incubation medium (Holtzman et al., 1980b). In view of the fact that Ca^{2+} uptake and entry into the mitochondrial matrix is also blocked by ruthenium red, it is possible that both lead and Ca^{2+} share the same binding site/carrier in brain mitochondria. These findings are supported by the work of Gmerek et al. (1981) on adult rat cerebral mitochondria, with the exception that they observed respiratory inhibition at 5 μM lead acetate, which is a full order of magnitude lower than the Holtzman et al. (1978b, 1980b) studies. Gmerek and co-workers offer the possibility that this discrepancy may have been due to the inadvertent presence of EDTA in the incubation medium used by Holtzman et al.

Organolead compounds have also been demonstrated to have a deleterious effect on cellular metabolism in the nervous system. For example, Grundt and Neskovic (1980) found that concentrations of triethyl lead chloride as low as 5-7 μM caused a 40 percent decrease in the incorporation of SO_4 or serine into myelin galacto-lipids in cerebellar slices from 2-week-old rats. Similarly, Konat and coworkers (Konat and Clausen, 1978, 1980; Konat et al., 1979) observed that 3 μM triethyl lead chloride preferentially inhibited the incorporation of leucine into myelin proteins in brain stem and forebrain slices from 22-day-old rats. This apparent inhibition of myelin protein synthesis was two-fold greater than that observed for total protein synthesis (approximately 10 vs. 20 percent, respectively). In addition, acute intoxication of these animals by i.p. injection of triethyl lead chloride at 8 mg/kg produced equivalent results accompanied by a 30 percent reduction in total forebrain myelin content.

Interestingly, while a suspension of cells from the forebrain of these animals (Konat et al., 1978) exhibited a 30 percent inhibition of total protein synthesis at 20 μM triethyl lead chloride (the lowest concentration examined), a cell-free system prepared from the same tissue was not affected by triethyl lead chloride concentrations as high as 200 μM. This result, coupled with a similar, although not as severe, inhibitory effect of triethyl lead chloride on oxygen consumption in the cell suspension (20 percent inhibition at 20 μM) would tend to indicate that the inhibition of rat forebrain protein synthesis is related to an inhibition of cellular energy-generating systems.

The effects of organolead compounds on various neurotransmitter systems have been investigated in adult mouse brain homogenates. Bondy et al. (1979a,b) demonstrated that micromolar concentrations (5 μM) of tri-n-butyl lead (TBL) acetate were sufficient not only to cause a 50 percent decline in the high affinity uptake of GABA and DA in such homogenates, but also to stimulate a 25 percent increase in GABA and DA release. These effects were apparently selective for DA neurons at lower concentrations, as only DA uptake or release was affected at 0.1 μM, albeit mildly so. The effect of TBL acetate on DA uptake appears to be specific, as there is a clear dose-response relationship down to 1 μM TBL (Bondy and Agarwal, 1980) for inhibition (0-60 percent) of spiroperidol binding to rat striatal DA receptors. A concomitant

inhibition of adenyl cyclase in this dose range (50 percent) suggests that TBL may affect the entire postsynaptic binding site for DA.

12.4.3.5 Accumulation and Retention of Lead in the Brain. All too infrequently, experimental studies of the neurotoxic effects of lead exposure do not report the blood-lead levels achieved by the exposure protocols used. Even less frequently reported are the concomitant tissue levels found in brain or other tissues. From the recent information that is available, however, it is possible to draw some limited conclusions about the relationship of exposure concentrations to blood and brain lead concentrations. Table 12-8 calculates the blood lead/brain lead ratios found in recent studies where such information was available. It can be seen that, at exposure concentrations greater than 0.2 percent and for exposure periods longer than birth until weaning (21 days in rats), the ratio generally falls below unity. This suggests, that, even as blood lead levels reach a steady state and then fall due to excretion or some other mechanism, lead continues to accumulate in brain.

Further evidence bearing on this was derived from a set of studies by Goldstein et al. (1974), who reported that administration of a wide range of doses of radioactive lead nitrate to one-month-old rats resulted in parallel linear increases in both blood and brain lead levels during the ensuing 24 hours. This suggests that deposition of lead in brain occurs without threshold and that, at least initially, it is proportional to blood lead concentration. However, further studies by Goldstein et al. (1974) followed changes in blood and brain lead concentrations after cessation of lead exposure and found that, whereas blood lead levels decreased dramatically (by an order of magnitude or more) during a 7-day period, brain lead levels remained essentially constant over the one-week postexposure period. Thus, with even intermittent exposures to lead, it is not unexpected that brain concentrations would tend to remain the same or even to increase although blood lead levels may have returned to "normal" levels. Evidence confirming this comes from findings of: (1) Hammond (1971), showing that EDTA administration causing marked lead excretion in urine of young rats did not significantly lower brain lead levels in the same animals; and (2) Goldstein et al. (1974), showing that although EDTA prevented the in vitro accumulation of lead into brain mitochondria, if lead was added first then EDTA was ineffective in removing lead from the mitochondria. These results, overall, indicate that, although lead may enter the brain in rough proportion to circulating blood lead concentrations, it is then taken up by brain cells and tightly bound into certain subcellular components (such as mitochondrial membranes) and retained there for quite long after initial external exposure ceases and blood lead levels markedly decrease. This may help to account for the persistence of neurotoxic effects of various types noted above long after the cessation of external lead exposure.

TABLE 12-8. INDEX OF BLOOD LEAD AND BRAIN LEAD LEVELS FOLLOWING EXPOSURE

Species (strain)	Exposure	Time of assay	Blood lead (µg/dl)	Brain lead (µg/100g)	Blood:brain lead ratio	Reference
Suckling rat (Charles River-CD)	0.0005% $PbCl_2$ in water PND 0-21	PND 21	12	8	1.5	Bull et al. (1979)
	0.003% $PbCl_2$ in water PND 0-21	PND 21	21	11	1.9	
Suckling rat (Charles River)	0.005% $Pb(Ac)_2$ in water from conception	PND 11 PND 30	22 18	3 11	7.0 1.6	Grant et al. (1980)
	0.01% $Pb(Ac)_2$ in water from conception	PND 11 PND 30	35 48	7 22	5.0 2.2	
Suckling rat (Charles River-CD)	0.02% $PbCl_2$ in water PND 0-21	PND 21	36	25	1.4	Bull et al. (1979)
Suckling rat (Long-Evans)	0.02% $Pb(Ac)_2$ in water PND 0-21	PND 10 PND 21	21.7 25.2	6.3 13	3.4 1.9	Fox et al. (1979)
Suckling rat (Long-Evans)	0.02% $Pb(Ac)_2$ in water from PND 0-21	PND 21	29	29	1.0	Hastings et al. (1979)
Suckling rat (Holtzman-albino)	0.05% $Pb(Ac)_2$ in water PND 0-21	PND 21	12	20	0.6	Goldman et al. (1980)
	0.1% $Pb(Ac)_2$ in water PND 0-21	PND 21	20	50	0.4	
Suckling rat	0.2% $Pb(Ac)_2$ in water PND 0-21	PND 21	65	65	1.0	Hastings et al. (1979)
Suckling rat (Holtzman-albino)	0.2% $Pb(Ac)_2$ in water PND 0-21	PND 21	47	80	0.6	Goldman et al. (1980)
Suckling rat (Long-Evans)	0.2% $Pb(Ac)_2$ in water PND 0-21	PND 10 PND 21	49.6 89.4	19 82	2.6 1.1	Fox et al. (1979)
Suckling rat (Long-Evans)	0.2% $Pb(Ac)_2$ in water PND 0-21	PND 21	65.0	53	1.2	Fox et al. (1977)
Suckling rat (Long-Evans)	0.2% $Pb(Ac)_2$ in water PND 0-21	PND 21	65.1	53	1.2	Cooper et al. (1980)
Suckling mice (ICR Swiss albino)	0.25% $Pb(Ac)_2$ in water PND 0-21	PND 21	72	230	0.3	Modak et al. (1978)
Suckling rat (Wistar)	0.2% $Pb(Ac)_2$ in water PND 2-60	PND 30 PND 60	115* 35*	84 99	- -	Shigeta et al. (1979)
	0.5% $Pb(AC)_2$ in water PND 2-60	PND 30 PND 60	308* 73*	172 222	- -	

Table 12-8. (continued)

Species (strain)	Exposure	Time of assay	Blood lead (µg/dl)	Brain lead (µg/100g)	Blood:brain lead ratio	Reference
Suckling rat (Sprague-Dawley)	0.25% $Pb(Ac)_2$ in water from gestation until PND 42	PND 42	87	85	1.0	Govani et al. (1980)
	0.5% $Pb(Ac)_2$ in water PND 0-21	PND 21	70	280	0.25	
	1% $Pb(Ac)_2$ in water PND 0-21	PND 21	91	270	0.3	
Suckling rat (Sprague-Dawley)	4% $PbCO_3$ in water PND 0-27	PND 27	---	1.36	---	Wince et al. (1980)
Suckling rat (Long-Evans)	25 mg/kg $Pb(Ac)_2$ by gavage PND 2-14	PND 15	50	40	1.3	Jason and Kellogg (1981)
	75 mg/kg $Pb(Ac)_2$ by gavage PND 2-14	PND 15	98	60	1.6	
Young mice (ICR Swiss albino)	0.25% $Pb(Ac)_2$ in water PND 0-60	PND 60	91	410	0.2	Modak et al. (1978)
	0.5% $Pb(Ac)_2$ in water PND 0-60	PND 60	194	360	0.5	
	1% $Pb(Ac)_2$ in water PND 0-60	PND 60	223	810	0.3	
Adult rat (Charles River-CD)	0.0005% $Pb(Ac)_2$ in water for 21 days		9	10	0.9	Bull et al. (1979)
	0.003% $Pb(Ac)_2$ in water for 21 days		11	12	0.9	
	0.02% $Pb(Ac)_2$ in water for 21 days		29	100	0.29	
Adult rat (Wistar)	0.15% $Pb(Ac)_2$ in water for 3 months		31	12-18 (depending on region)	2.6-1.7 (depending on region)	Ewers and Erbe (1980)
	0.4% $Pb(Ac)_2$ in water for 3 months		69	16-34 (depending on region)	4.3-2.0 (depending on region)	
	1% $Pb(Ac)_2$ in water for 3 months		122	37-72 (depending on region)	3.3-1.7 (depending on region)	

PND: post-natal day

$Pb(Ac)_2$: lead acetate

$PbCl_2$: lead chloride

*Expressed as µg Pb/100g blood.

The uptake of lead into specific neural and non-neuronal elements of the brain has also been studied and provides insight into possible morphological correlates of certain lead effects discussed above and below as being observed in vivo or in vitro. For example, Stumpf et al. (1980), via autoradiographic localization of ^{210}Pb, found that ependymal cells, glial cells, and endothelial cells of brain capillaries concentrate and retain lead above background levels for several days after injections of tracer amounts of the elements. These cells are non-neural elements of brain important in the maintenance of "blood-brain barrier" functions, and their uptake and retention of lead, even with tracer doses, provides evidence of a morphological basis by which lead effects on blood-brain barrier functions may be exerted. Again, the retention of lead in these non-neuronal elements for at least several days after original exposure points towards the plausibility of lead exerting effects on blood-brain barrier functions long after external exposure ceases and blood lead levels decrease back toward normal levels. Uptake and concentration of lead in the nuclei of some cortical neurons even several days after administration of only a tracer dose of ^{210}Pb was also observed by Stumpf et al. (1980) and provide yet another plausible morphological basis by which neurotoxic effects might be exerted by lead long after external exposure terminates and blood lead levels return to apparently "normal" levels.

12.4.4 Integrative Summary of Human and Animal Studies of Neurotoxicity

An assessment of the impact of lead on human and animal neurobehavioral function raises a number of issues. Among the key points addressed here are: (1) the internal exposure levels, as indexed by blood lead levels, at which various adverse neurobehavioral effects occur; (2) the reversibility of such deleterious effects; and (3) the populations that appear to be most susceptible to neural damage. In addition, the question arises as to the utility of using animal studies to draw parallels to the human condition.

12.4.4.1 Internal Exposure Levels at Which Adverse Neurobehavioral Effects Occur. Markedly elevated blood lead levels are associated with neurotoxic effects of lead exposure (including severe, irreversible brain damage as indexed by the occurrence of acute and/or chronic encephalopathic symptoms) in both humans and and animals. For most adult humans, such damage typically does not occur until blood lead levels exceed 120 µg/dl. Evidence does exist, however, for acute encephalopathy and death occurring in some human adults at blood lead levels below 120 µg/dl. In children, the effective blood lead level for producing encephalopathy or death is lower, starting at approximately 100 µg/dl. Again, however, evidence exists for encephalopathy occurring in some children at lower blood lead levels, i.e., at 80-100 µg/dl.

It should be emphasized that, once encephalopathy occurs, death is not an improbable outcome, regardless of the quality of medical treatment available at the time of acute crisis.

In fact, certain diagnostic or treatment procedures themselves tend to exacerbate matters and push the outcome toward fatality if the nature and severity of the problem are not fully recognized or properly diagnosed. It is also crucial to note the rapidity with which acute encephalopathic symptoms can develop or death can occur in apparently asymptomatic individuals or in those apparently only mildly affected by elevated body burdens of lead. It is not unusual for rapid deterioration to occur, with convulsions or coma suddenly appearing and with progression to death within 48 hours. This strongly suggests that, even in apparently asymptomatic individuals, rather severe neural damage probably does exist at high blood lead levels even though it is not yet overtly manifested in obvious encephalopathic symptoms. This conclusion is further supported by numerous studies showing that children with high blood lead levels (over 80-100 μg/dl), but not observed to manifest acute encephalopathic symptoms, are permanently cognitively impaired, as are most children who survive acute episodes of frank lead encephalopathy.

Other evidence tends to confirm that some type of neural dysfunction exists in apparently asymptomatic children, even at much lower levels of blood lead. The body of studies on low- or moderate-level lead effects on neurobehavioral functions, as summarized in Table 12-1, presents a rather impressive array of data pointing to that conclusion. Several well-controlled studies have found effects that are clearly statistically significant, whereas others have found nonsignificant but borderline effects. Even certain studies reporting generally nonsignificant findings at times contain data confirming some statistically significant effects, which the authors attribute to various extraneous factors. It should also be noted that, given the apparent non-specific nature of some of the behavioral or neural effects probable at low levels of lead exposure, one would not expect to find striking differences in every instance. The lowest blood lead levels associated with significant neurobehavioral (e.g. cognitive) deficits both in apparently asymptomatic children and in developing rats and monkeys generally appear to be in the range of 30-50 μg/dl. Also, certain behavioral and electrophysiological effects indicative of CNS deficits have been reported at lower levels, supporting a continuous dose-response relationship between lead and neurotoxicity. Such effects, when combined with adverse social factors (such as low parental IQ, low socioeconomic status, poor nutrition, and poor quality of the caregiving environment) can place children, especially those below the age of three years, at significant risk. However, it must be acknowledged that nutritional covariates, as well as demographic social factors, have been poorly controlled in many of the pediatric neurobehavioral studies reviewed above. Socioeconomic status also is a crude measure of parenting and family structure that requires further assessment as a possible contributor to observed results of neurobehavioral studies.

Timing, type, and duration of exposure are also important factors in both animal and human studies. It is often uncertain whether observed blood lead levels represent the levels that were responsible for observed behavioral deficits. Monitoring of lead exposures in human subjects in all cases has been highly intermittent or non-existent during the period of life preceding neurobehavioral assessment. In most human studies, only one or two blood lead values are provided per subject. Tooth lead may be an important cumulative exposure index; but its modest, highly variable correlation to blood lead or FEP and to external exposure levels makes findings from various studies difficult to compare quantitatively. The complexity of the many important covariates and their interaction with dependent measures of modest validity, e.g., IQ tests, may also account for many of the discrepancies among the different studies.

The precise medical or health significance of the neuropsychological and electrophysiological effects associated with low-level lead exposure as reported in the above studies is difficult to state with confidence at this time. Observed IQ deficits and other behavioral changes, although statistically significant in some studies, tend to be relatively small as reported by the investigators, but nevertheless may still affect the intellectual development, school performance, and social development of the affected children sufficiently to be regarded as adverse. This would be especially true if such impaired intellectual development or school performance and disrupted social development were reflective of persisting, long-term effects of low-level lead exposure in early childhood. The issue of persistence of such lead effects, however, remains to be more clearly resolved. Still, some study results reviewed above suggest that significant low-level lead-induced neurobehavioral and EEG effects may, in fact, persist at least into later childhood, and a number of animal studies demonstrate long-term persistence into adulthood of neurologic dysfunctions induced by relatively moderate or low level lead exposures early in postnatal development of mammalian species.

12.4.4.2 The Question of Irreversibility. Little research on humans is available on persistence of effects. Some work suggests the possibility of reversing mild forms of peripheral neuropathy in lead workers, but little is known regarding the reversibility of lead effects on central nervous system function in humans. A recent two-year follow-up study of 28 children of battery factory workers found a persistent relation between blood lead and altered slow wave voltage of cortical slow wave potentials. Current human psychometric studies, however, will have to be supplemented by prospective longitudinal studies of the effects of lead on development in order to better elucidate persistence or reversibility of neurotoxic effects of lead exposure early in infancy or childhood.

Various animal studies provide evidence that alterations in neurobehavioral function may be long-lived, with such alterations being evident long after blood lead levels have returned

to control levels. These persistent effects have been demonstrated in monkeys as well as rats under a variety of learning performance test paradigms. Such results are also consistent with morphological, electrophysiological, and biochemical studies on animals that suggest lasting changes in synaptogenesis, dendritic development, myelin and fiber tract formation, ionic mechanisms of neurotransmission, and energy metabolism.

12.4.4.3 Early Development and Susceptibility to Neural Damage. On the question of early childhood vulnerability, the neurobehavioral data are consistent with morphological and biochemical studies of the susceptibility of the heme biosynthetic pathway to perturbation by lead. Various lines of evidence suggest that the order of susceptibility neurotoxic effects of lead is: young > adult; female > male. Animal studies also have pointed to the perinatal period of ontogeny as a particularly critical time for a variety of reasons: (1) it is a period of rapid development of the nervous system; (2) it is a period where good nutrition is particularly critical; and (3) it is a period where the caregiver environment is vital to normal development. However, the precise boundaries of a critical period for lead exposure are not yet clear and may vary depending on the species and function or endpoint that is being assessed. Nevertheless, there is general agreement that human infants and toddlers below the age of three years are at special risk because of in utero exposure, increased opportunity for exposure because of normal mouthing behavior of lead-containing objects, and increased rates of lead absorption due to various factors, e.g., iron and calcium deficiencies.

12.4.4.4 Utility of Animal Studies in Drawing Parallels to the Human Condition. Animal models are used to shed light on questions where it would be impractical or ethically unacceptable to use human subjects. This is particularly true in the case of exposure to environmental toxins such as lead. In the case of lead, it has been most effective and convenient to expose developing animals via their mothers' milk or by gastric gavage, at least until weaning. Very often, the exposure is continued in the water or food for some time beyond weaning. This approach does succeed in simulating at least two features commonly found in human exposure: oral intake and exposure during early development. The preweaning postnatal period in rats and mice is of particular relevance in terms of parallels with the first two years or so of human brain development.

However, important questions exist concerning the comparability of animal models to humans. Given differences between humans, rats, and monkeys in heme chemistry, metabolism, and other aspects of physiology and anatomy, it is difficult to state what constitutes an equivalent internal exposure level (much less an equivalent external exposure level). For example, is a blood lead level of 30 µg/dl in a suckling rat equivalent to 30 µg/dl in a three-year-old child? Until an answer is available to this question, i.e., until the function describing the relationship of exposure indices in different species is available, the utility of animal models for deriving dose-response functions relevant to humans will be limited.

Questions also exist regarding the comparability of neurobehavioral effects in animals with human behavior and cognitive function. One difficulty in comparing behavioral endpoints such as locomotor activity is the lack of a consistent operational definition. In addition to the lack of standardized methodologies, behavior is notoriously difficult to "equate" or compare meaningfully across species because behavioral analogies do not demonstrate behavioral homologies. Thus, it is improper to assume, without knowing more about the responsible underlying neurological structures and processes, that a rat's performance on an operant conditioning schedule or a monkey's performance on a stimulus discrimination task necessarily corresponds directly to a child's performance on a cognitive function test. Nevertheless, deficits in performance by mammalian animals on such tasks are indicative of likely altered CNS functions, which is reasonable to assume will likely parallel some type of altered CNS function in humans as well.

In terms of morphological findings, there are reports of hippocampal lesions in both lead-exposed rats and humans that are consistent with a number of independent behavioral findings suggesting an impaired ability to respond appropriately to altered contingencies for rewards. That is, subjects with hippocampal damage tend to persist in certain patterns of behavior even when changed conditions make the behavior inappropriate; the same sort of tendency seems to be common to a number of lead-induced behavioral effects. Other morphological findings in animals, such as demyelination and glial cell decline, are comparable to human neuropathologic observations only at relatively high exposure levels.

Another neurobehavioral endpoint of interest in comparing human and animal neurotoxicity of lead is electrophysiological function. Alterations of electroencephalographic patterns and cortical slow wave voltage have been reported for lead-exposed children, and various electrophysiological alterations both *in vivo* (e.g., in rat visual evoked response) and *in vitro* (e.g., in frog miniature endplate potentials) have also been noted in laboratory animals. Thus, far, however, these lines of work have not converged sufficiently to allow for much in the way of definitive conclusions regarding electrophysiological aspects of lead neurotoxicity.

Biochemical approaches to the experimental study of lead effects on the nervous system have been basically limited to laboratory animal subjects. Although their linkage to human neurobehavioral function is at this point somewhat speculative, such studies do provide insight on possible neurochemical intermediaries of lead neurotoxicity. No single neurotransmitter system has been shown to be particularly sensitive to the effects of lead exposure; lead-induced alterations have been demonstrated in various neurotransmitters, including dopamine, norepinephrine, serotonin, and gamma-aminobutyric acid. In addition, lead has been shown to have subcellular effects in the central nervous system at the level of mitochondrial function and protein synthesis. In particular, the work of McCauley, Bull, and co-workers has

indicated that delays seen in cortical synoptogenesis and metabolic maturation following prenatal lead exposure may well underly the delayed development of exploratory and locomoter function seen in other studies of the neurobehavioral effects of lead.

Given the difficulties in formulating a comparative basis for internal exposure levels among different species, the primary value of many animal studies, particularly in vitro studies, may be in the information they can provide on basic mechanisms involved in lead neurotoxicity. A number of key in vitro studies are summarized in Table 12-9. These studies show that significant, potentially deleterious effects on nervous system function occur at in situ lead concentrations of 5 μM and possibly lower. This suggests that, at least intracellularly or on a molecular level, there may exist essentially no threshold for certain neurochemical effects of lead. The relationship between blood lead levels and lead concentrations at extra- or intracellular sites of action, however, remains to be determined.

Despite the problems in generalizing from animals to humans, both the animal and the human studies show considerable internal consistency in that they both support a continuous dose-response functional relationship between lead and neurotoxic biochemical, morphological, electrophysiological, and behavioral effects.

TABLE 12-9. SUMMARY OF KEY STUDIES OF IN VITRO LEAD EXPOSURE

Preparation	Exposure concentration	Results	Reference
Adult rat brain	0.1 μM $Pb(Ac)_2$	35% inhibition of whole-brain BH_4 synthesis	Purdy et al. (1981)
Isolated microvessels from rat brain	0.1 μM $Pb(Ac)_2$	Blockade of sugar-specific transport sites in capillary endothelial cells	Kolber et al. (1980)
Adult mouse brain homogenate	0.1-5 μM tri-n-butyl lead (TBL)	1) 50% decline in high affinity uptake of DA; 2) 25% increase in release of DA	Bondy et al. (1979a,b)
Adult rat striatum	1-5 μM TBL	0-60% inhibition of spiroperidal binding to DA receptors	Bondy and Agarwal (1980)
Embryonic chick brain cell culture	3 μM $(Et_3Pb)Cl_2$	50% reduction in no. of cells exhibiting processes	Grundt et al. (1981)
Brainstem and forebrain slices from PND-22 rats	3 μM $(Et_3Pb)Cl_2$	Inhibition of leucine incorporation into myelin proteins	Konat and Clausen (1978, 1980) Konat et al. (1979)
Adult rat cerebellar homogenates	3-5 μM Pb^{++}	Inhibition of adenylate cyclase activity	Taylor et al. (1978)
Adult rat cerebellar mitochondria	5 μM $Pb(Ac)_2$	Inhibition of respiration	Gmerek et al. (1981)
Adult frog nerve/muscle preparation	5 μM Pb^{++}	Increase in frequency of MEPP's (indicative of depression of synaptic transmission)	Kolton and Yaari (1982)
Isolated, perfused bullfrog retina	5 μM Pb^{++}	Depression of rod (but not cone) receptor potentials	Fox and Sillman (1979)

TABLE 12-9. (continued)

Preparation	Exposure concentration	Results	Reference
Cerebellar slices from PND-14 rats	5-7 μM $(Et_3Pb)Cl_2$	Inhibition of incorporation of SO_4 and serine into myelin galactolipids	Grundt and Neskovic (1980)
In oculo culture of cerebellar tissue from PND-15 rats	5-10 μM Pb^{++}	"Disinhibition" of NE-induced inhibition of spontaneous activity in Purkinje cells	Taylor et al. (1978)
Cell suspension from forebrain of PND-22 rats	20 μM $(Et_3Pb)Cl_2$	30% inhibition of total protein synthesis	Konat et al. (1978)
Adult rat cerebral and cerebellar mitochondria	50 μM $Pb(Ac)_2$	Inhibition of respiration	Holtzman et al. (1978b, 1980b)
Adult rat caudate synaptosomes	50 μM $PbCl_2$	8-fold increase in binding of Ca^{++} to mitochondria (effectively increases Ca^{++} gradient across terminal membrane, thus increasing synatic transmission without altering firing rates)	Silbergeld and Adler (1978)
Capillary endothelial cells from rat cerecortex	100 μM $Pb(Ac)_2$	Pb preferentially sequestered in mitochondria like Ca^{++}. (Possible basis for Pb-induced disruption of transmembrane Ca^{++} transport)	Silbergeld et al. (1980b)

PND: post-natal day
$Pb(Ac)_2$: lead acetate
$PbCl_2$: lead chloride
Et_3Pb: triethyl lead
TBL: tri-n-butyl lead
DA: dopamine
NE: norepinephrine
BH_4: tetrahydrobiopterin
MEPP's: miniature endplate potentials

12.5 EFFECTS OF LEAD ON THE KIDNEY

12.5.1 Historical Aspects

The first description of renal disease due to lead was published by Lancereaux (1862). In a painter with lead encephalopathy and gout, Lancereaux noted tubulo-interstitial disease of the kidneys at autopsy. Distinctions between glomerular and tubulo-interstitial forms of kidney disease were not, however, clearly defined in the mid-nineteenth century. Ollivier (1863) reported observations in 37 cases of lead poisoning with renal disease and thus introduced the idea that lead nephropathy was a proteinuric disease, a confusion with primary glomerular disease that persisted for over a century. Under the leadership of Jean Martin Charcot, interstitial nephritis characterized by meager proteinuria in lead poisoning was widely publicized (Charcot, 1868; Charcot and Gombault, 1881) but not always appreciated by contemporary physicians (Danjoy, 1864; Gepper, 1882; Lorimer, 1886).

More than ninety years ago, the English toxicologist Thomas Oliver (1885, 1891) distinguished acute effects of lead on the kidney from lead-induced chronic nephropathy. Acute renal effects of lead were seen in persons dying of lead poisoning and were usually restricted to non-specific changes in the renal proximal tubular lining cells. Oliver noted that a "true interstitial nephritis" developed later, often with glomerular involvement.

In an extensive review of the earlier literature, Pejić (1928) emphasized that changes in the proximal tubules, rather than the vascular changes often referred to in earlier studies (Gull and Sutton, 1872), constitute the primary injury to the kidney in lead poisoning. Many subsequent studies have shown pathological alterations in the renal tubule with onset during the early or acute phase of lead intoxication. These include the formation of inclusion bodies in nuclei of proximal tubular cells (Blackman, 1936) and the development of functional defects as well as ultrastructural changes, particularly in renal tubular mitochondria.

12.5.2 Lead Nephropathy in Childhood

Dysfunction of the proximal tubule was first noted as glycosuria in the absence of hyperglycemia in childhood pica (McKhann, 1926). Later it was shown that the proximal tubule transport defect included aminoaciduria (Wilson et al., 1953). Subsequently, Chisolm et al. (1955) found that the full Fanconi syndrome was present: glycosuria, aminoaciduria, phosphaturia (with hypophosphatemia), and rickets. Proximal tubular transport defects appeared only when blood lead levels exceeded 80 µg/dl. Generalized aminoaciduria was seen more consistently in Chisolm's (1962, 1968) studies than were other manifestations of renal dysfunction. The condition was related to the severity of clinical toxicity, with the complete Fanconi syndrome occurring in encephalopathic children when blood lead concentrations exceeded 150 µg/dl (National Academy of Sciences, 1972). Children who were under three years of age excreted 4 to 12.8 mg of lead chelate during the first day of therapy with CaEDTA at 50 mg/kg

day. The aminoaciduria disappeared after treatment with chelating agents and clinical remission of other symptoms of lead toxicity (Chisolm, 1962). This is an important observation relative to the long-term or chronic effects of lead on the kidney.

In a group of children with slight lead-related neurological signs reported by Pueschel et al. (1972), generalized aminoaciduria was found in 8 of 43 children with blood lead levels of 40 to 120 µg/dl. It should be noted that the children reported to have aminoaciduria in this study were selected because of a blood lead level of ≧50 µg/dl or a provocative chelation test of >500 µg of lead chelate per 24 hours.

Although children are considered generally to be more susceptible than adults to the toxic effects of lead, the relatively sparse literature on childhood lead nephropathy probably reflects a greater clinical concern with the life-threatening neurologic symptoms of lead intoxication than with the transient Fanconi syndrome.

12.5.3 Lead Nephropathy in Adults

There is convincing evidence in the literature that prolonged lead exposure in humans can result in chronic lead nephropathy in adults. This evidence is reviewed below in terms of six major categories: (1) lead nephropathy following childhood lead poisoning; (2) "moonshine" lead nephropathy; (3) occupational lead nephropathy; (4) lead and gouty nephropathy; (5) lead and hypertensive nephrosclerosis; and (6) general population studies.

12.5.3.1 Lead Nephropathy Following Childhood Lead Poisoning. Reports from Queensland, Australia (Gibson et al., 1892; Nye, 1933; Henderson, 1954; Emmerson, 1963) points to a strong association between severe childhood lead poisoning, including central nervous system symptoms, and chronic nephritis in early adulthood. The Australian children sustained acute lead poisoning when confined to the enclosed, raised terraces peculiar to the houses around Brisbane. The houses were painted with white lead, which the children ingested by direct contamination of their fingers or by drinking lead-sweetened rain water as it flowed over the weathered surfaces. Two fingers brushed against the powdery paint were shown to pick up about 2 mg of lead (Murray, 1939). Henderson (1954) followed up 401 untreated children who had been diagnosed as having lead poisoning in Brisbane between 1915 and 1935. Of these 401 subjects, death certificates revealed that 165 had died under the age of 40, 108 from nephritis or hypertension. This is greatly in excess of expectation. Information was obtained from 101 of the 187 survivors, and 17 of these had hypertension and/or albuminuria.

In a more recent study, Emmerson (1963) presented a criterion for implicating lead as an etiological factor in such patients: the patients should have an excessive urinary excretion of lead following administration of CaEDTA. Leckie and Tompsett (1958) had shown that increasing the CaEDTA dosage above 2 g/day intravenously had little effect on the amount of lead chelate excreted by adults. They observed little difference in chelatable lead excretion

when 1 g was compared with 2 g (i.v.). Similarly, the magnitude of lead chelated when 1 g is given i.v. or 2 g i.m. (over 12 hr) appears to be the same (Albahary et al., 1961; Emmerson, 1963; Wedeen et al., 1975). Adult control subjects without undue lead absorption excrete less than 650 µg lead chelate during the first post-injection day if renal function is normal, or over 4 days if renal function is severely reduced. The level of reduction of glomerular filtration rate (GFR) at which the EDTA lead-mobilization test is no longer reliable has not been precisely defined but probably exceeds a reduction of 85 percent (serum creatinine concentrations in excess of about 6 mg/dl). In Emmerson's (1963) study 32 patients with chronic renal disease attributable to lead poisoning had elevated excretion of lead chelate. Intranuclear inclusions are associated with recent acute exposure but are often absent in chronic lead nephropathy or after the administration of $CaNa_2EDTA$ (Goyer and Wilson, 1975).

The Australian investigators established the validity of the EDTA lead-mobilization test for the detection of excessive past lead absorption and further demonstrated that the body lead stores were retained primarily in bone (Emmerson, 1963; Henderson, 1954; Inglis et al., 1978). Bone lead concentration averaged 94 µg/g wet weight in the young adults dying of lead nephropathy in Australia (Henderson and Inglis, 1957; Inglis et al., 1978), compared with mean values ranging from 14 to 23 µg/g wet weight in bones from non-exposed individuals (Barry, 1975; Emmerson, 1963; Gross et al., 1975; Wedeen, 1982).

Attempts to confirm the relationship between childhood lead intoxication and chronic nephropathy have not been successful in at least two studies in the United States. Tepper (1963) found no evidence of increased chronic renal disease in 139 persons with a well-documented history of childhood plumbism 20 to 35 years earlier at the Boston Children's Hospital. The study population was 165 patients (after review of 524 case records) who met any two of the following criteria: 1) a definite history of pica or use of lead nipple shields; 2) X-ray evidence of lead-induced skeletal alterations; or 3) characteristic symptoms. No uniform objective measure of lead absorption was reported in this study. In 42 of the 139 subjects clinical studies of renal function were performed and included urinalysis, endogenous creatinine clearance, urine culture, urine concentrating ability, 24-hour protein excretion, and phenolsulfonphthalein excretion. Only one patient was believed to have died of lead nephropathy; three with creatinine clearances under 90 ml/min were said to have had inadequate urine collections. Insufficient details concerning past lead absorption and patient selection were provided to permit generalized conclusions from this report.

Chisolm et al. (1976) also found no evidence of renal disease (as judged by routine urinalysis, blood urea nitrogen, serum uric acid, and creatinine clearance) in 55 adolescents known to have been treated for lead intoxication 11 to 16 years earlier. An important distinction between the Australian group and those patients in the United States studied by Chisolm et al. (1976) was that none of the latter subjects showed evidence of increased

residual body lead burden by the EDTA lead-mobilization test. This U.S. study was carried out on adolescents between 12 and 22 years of age in the late 1960s. During acute toxicity in early childhood, blood lead levels had ranged from 100 to 650 µg/dl; all received immediate chelation therapy. Follow-up chelation tests performed with 1 g EDTA i.m. (with procaine) approximately a decade later resulted in 24-hour lead-chelate excretion of less than 600 µg in 45 of 52 adolescents. The absence of renal disease in this study led Chisolm et al. to suggest that lead toxicity in the Australian children may have been of a different type, with a more protracted course than that experienced by the American children. On the other hand, chelation therapy of the American children may have removed lead stored in bone and thus prevented the development of renal failure later in life. Most children in the United States who suffer from overt lead toxicity do so early in childhood, between the ages of 1 and 4, the source often being oral ingestion of flecks of wall paint and plaster containing lead.

12.5.3.2 "Moonshine" Lead Nephropathy. In the United States, chronic lead nephropathy in adults was first noted among illicit whiskey consumers in the southeastern states. The prerevolutionary tradition of homemade whiskey ("moonshine") was modernized during the Prohibition era for large scale production. The copper condensers traditionally used in the illegal stills were replaced by truck radiators with lead-soldered parts. Illegally produced whiskey might contain up to 74 mg of lead per liter (Eskew et al., 1961). The enormous variability in moonshine lead content has recently been reiterated in a study of 12 samples from Georgia, of which five contained less than 10 µg/l but one contained 5.3 mg/l (Gerhardt et al., 1980).

Renal disease often accompanied by hypertension and gout was common among moonshiners (Eskew et al., 1961; Morgan et al., 1966; Ball and Sorenson, 1969). These patients usually sought medical care because of symptomatic lead poisoning characterized by colic, neurological disturbances, and anemia, although more subtle cases were sometimes detected by use of the i.v. EDTA lead-mobilization test (Morgan, 1968; Morgan and Burch, 1972). While acute symptomatology, including azotemia, sometimes improved during chelation therapy, residual chronic renal failure, gout, and hypertension frequently proved refractory, thus indicating underlying chronic renal disease superimposed on acute renal failure due to lead (Morgan, 1975).

12.5.3.3 Occupational Lead Nephropathy. Although rarely recognized in the United States (Brieger and Reiders, 1959; Anonymous, 1966; Greenfield and Gray, 1950; Johnstone, 1964; Kazantzis, 1970; Lane, 1949; Malcolm, 1971; Mayers, 1947), occupational lead nephropathy, often associated with gout and hypertension, was widely identified in Europe as a sequela to overt lead intoxication in the industrial setting (Albahary et al., 1961, 1965; Cramer et al., 1974; Danilović, 1958; Galle and Morel-Maroger, 1965; Lejeune et al., 1969; Lilis et al., 1967, 1968; Radosević et al., 1961; Radulescu et al., 1957; Richet et al., 1964, 1966; Tara and Francon, 1975; Vigdortchik, 1935). Some important recent studies are summarized here.

Richet et al. (1964) reported renal findings in eight lead workers, all of whom had repeated episodes of lead poisoning, including colic. Intravenous EDTA lead-mobilization tests ranged from 587 to 5930 µg lead-chelate excretion per 24 hours. Four of these men had reduced glomerular filtration rates, one had hypertension with gout, one had hypertension alone, and one had gout alone. Proteinuria exceeded 200 mg/day in only one patient. Five of seven renal biopsies were abnormal showing minor glomerular sclerosis but severe interstitial nephritis and vascular sclerosis by light microscopy. The one patient with proteinuria of 1.7 gm/day showed extensive glomerular hyalinization. Electron microscopy showed intranuclear and cytoplasmic inclusions and ballooning of mitochondria in proximal tubule cells. The presence of intranuclear inclusion bodies is helpful in establishing a relationship between renal lesions and lead toxicity, but inclusion bodies are not always present in persons with chronic lead nephropathy (Cramer et al., 1974; Wedeen et al., 1975, 1979).

Richet et al. (1966) subsequently recorded renal findings in 23 symptomatic lead workers in whom blood lead levels ranged from 30 to 87 µg/dl. Six had diastolic pressures over 90 mm Hg, three had proteinuria exceeding 200 mg/day, and five had gout. In 5 of 21 renal biopsies, glomeruli showed minor hyalinization, but two cases showed major glomerular disease (their creatinine clearances were 20 and 33 ml/min, respectively). Interstitial fibrosis and arteriolar sclerosis were seen in all but two biopsies. Intranuclear inclusion bodies were noted in 13 cases. Electron microscopy showed loss of brush borders, iron-staining intracellular vacuoles, and ballooning of mitochondria in proximal tubule epithelial cells.

Effective renal plasma flow (C_{pah}, plasma clearance of p-aminohippuric acid) by the single injection disappearance technique was measured in 14 lead-poisoned Rumanian workers before and after chelation therapy by Lilis et al. (1967). C_{pah} increased from a pre-treatment mean of 428 ml/min (significantly less than the control mean of 580 ml/min) to a mean of 485 ml/min after chelation therapy ($p < 0.02$). However, no significant increase in GFR (endogenous creatinine clearance) was found. Lilis et al. interpreted the change in effective renal plasma flow as indicating reversal of the renal vasoconstriction that accompanied acute lead toxicity. Although neither blood lead concentrations nor long-term follow-up studies of renal function were provided, it seems likely that most of these patients suffered from acute, rather than chronic, lead nephropathy.

In a subsequent set of 102 cases of occupational lead poisoning studied by Lilis et al. (1968), seven cases of clinically verified chronic nephropathy were found. In this group, endogenous creatinine clearance was less than 80 ml/min two weeks or more after the last episode of lead colic. The mean blood lead level approximated 80 µg/dl (range 42 to 141 µg/dl.) All patients excreted more than 10 mg lead chelate over 5 days during therapy consisting of 2 g $CaNa_2EDTA$ i.v. daily. Nephropathy was more common among those exposed to lead for more than 10 years than among those exposed for less than 10 years. Most of the Rumanian lead workers

had experienced lead colic, and 13 of 17 had persistent hypertension that followed the appearance of renal failure by several years. Proteinuria was absent except in two individuals who excreted 250 and 500 mg/l. Hyperuricemia was not evident in the absence of azotemia. In both studies by Lillis, reduced urea clearance preceded reduced creatinine clearance.

Cramer et al. (1974) examined renal biopsies from five lead workers exposed for 0.5 to 20 years in Sweden. Their blood lead levels ranged from 71 to 138 µg/dl, with GFR ranging from 65 to 128 ml/min, but C_{pah} exceeding 600 ml/min in all. Although plasma concentrations of valine, tyrosine, and phenylalanine were reduced, excretion of these amino acids was not significantly different from controls. A proximal tubular reabsorptive defect might, therefore, have been present without increased amino acid excretion because of low circulating levels: increased fractional excretion may have occurred without increased absolute amino acid excretion. Albuminuria and glycosuria were not present. Glomeruli were normal by electron microscopy. Intranuclear inclusions in proximal tubules were found in two patients with normal GFRs, and peritubular fibrosis was present in the remaining three patients who had had the longest occupational exposure (4 to 20 years).

Wedeen et al. (1975, 1979) reported on renal dysfunction in 140 occupationally exposed men. These investigators used the EDTA lead-mobilization test (1 g CaEDTA with 1 ml of 2 percent procaine given i.m. twice, 8 to 12 hr apart) to detect workers with excessive body lead stores. In contrast to workers with concurrent lead exposure (Alessio et al., 1979), blood lead measures have proven unsatisfactory for detection of past lead exposure (Baker et al., 1979; Havelda et al., 1980; Vitale et al., 1975). Of the 140 workers tested, 113 excreted 1000 µg or more of lead-chelate in 24 hr compared with a normal upper limit of 650 µg/day (Albahary et al., 1961; Emmerson, 1973; Wedeen et al., 1975). Glomerular filtration rates measured by ^{125}I-iothalamate clearance in 57 men with increased mobilizable lead revealed reduced renal function in 21 (GFR less than 90 ml/min per 1.73 m^2 body surface area). When workers over age 55 or with gout, hypertension, or other possible causes of renal disease were excluded, 15 remained who had previously unsuspected lead nephropathy. Their GFRs ranged between 52 and 88 ml/min per 1.73 m^2. Only three of the men with occult renal failure had ever experienced symptoms attributable to lead poisoning. Of the 15 lead nephropathy patients, one had a blood lead level over 80 µg/dl, three repeatedly had blood levels under 40 µg/dl, and eleven had blood levels between 40 and 80 µg/dl at the time of the study. Thus, blood lead levels were poorly correlated with degree of renal dysfunction. The failure of blood lead level to predict the presence of lead nephropathy probably stems from the independence of blood lead from cumulative bone lead stores (Gross, 1981; Saenger et al., 1982a,b).

Percutaneous renal biopsies from 12 of the lead workers with reduced GFRs revealed focal interstitial nephritis in six. Non-specific changes were present in proximal tubules, including loss of brush borders, deformed mitochondria, and increased lysosomal bodies. Intra-

nuclear inclusion bodies were not found in the renal biopsies from these men who had experienced long-term occupational exposure and who had had chelation tests shortly before biopsy. In experimental animals, chelation results in the rapid disapperance of lead-induced intranuclear inclusions (Goyer and Wilson, 1975). The presence of a variety of immunoglobulin deposits by fluorescent microscopy suggests (but does not prove) the possibility that some stages of lead nephropathy in adults may be mediated by immune mechanisms.

Eight patients with pre-azotemic occupational lead nephropathy were treated with 1 g CaEDTA (with procaine) i.m. three times weekly for 6 to 50 months. In four patients, GFR rose by 20 percent or more by the time the EDTA test had fallen to less than 850 µg Pb/day. The rise in GFR was paralleled by increases in effective renal plasma flow (C_{pah}) during CaEDTA treatment. These findings indicate that chronic lead nephropathy may be reversible by chelation therapy, at least during the pre-azotemic phase of the disease (Wedeen et al., 1979). However, much more information will have to be obtained on the value of long-term, low-dose chelation therapy before this regimen can be widely recommended. There is, at present, no evidence that interstitial nephritis itself is reversed by chelation therapy. It may well be that only functional derangements are corrected and that the improvement in GFR is not accompanied by disappearance of tubulo-interstitial changes in kidney. Chronic volume depletion, for example, might be caused by lead-induced depression of the renin-angiotension-aldosterone system (McAllister et al., 1971) or by direct inhibition of (Na^+, K^+)ATPase-mediated sodium transport (Nechay and Williams, 1977; Nechay and Saunders, 1978a,b,c; Raghavan et al., 1981; Secchi et al., 1973). On the other hand, volume depletion would be expected to produce prerenal azotemia, but this was not evident in these patients. The value of chelation therapy in chronic lead nephropathy once azotemia is established is unknown.

The prevalence of azotemia among lead workers has recently been confirmed in health surveys conducted at industrial sites (Baker et al., 1979; Hammond et al., 1980; Landrigan et al., 1982; Lilis et al., 1979, 1980). Interpretation of these data is, however, hampered by the weak correlation generally found between blood lead levels and chronic lead nephropathy in adults, the absence of matched prospective controls, and the lack of detailed diagnostic information on the workers found to have renal dysfunction. Moreover, blood serum urea nitrogen (BUN) is a relatively poor indicator of renal function because it is sensitive to a variety of physiological variables other than GFR, including protein anabolism, catabolism, and hydration. Several other measures of renal function are more reliable than the BUN, including in order of increasing clinical reliability: serum creatinine, endogenous creatinine clearance, and ^{125}I-iothalamate or inulin clearance. It should be noted that none of these measures of GFR can be considered reliable in the presence of any acute illness such as lead colic or encephalopathy. Elevated BUN in field surveys may, therefore, sometimes represent transient acute functional changes rather than chronic intrinsic renal disease.

The variable susceptibility of the kidneys to the nephrotoxic effects of lead suggests that environmental factors in addition to lead may participate in the expression of renal damage. Industrial workers are often exposed to a variety of toxic materials, some of which, such as cadmium (Buchet et al., 1980), are themselves nephrotoxic. In contrast to cadmium, lead does not increase urinary excretion of beta-2-microglobulins (Batuman et al., 1981; Buchet et al., 1980) or lysozyme (Wedeen et al., 1979). Multiple interactions between environmental toxins may enhance susceptibility to lead nephrotoxicity. Similarly, nephrotoxicity may be modulated by reductions in 1,25-dihydroxy vitamin D_3, increased 6-beta-hydroxycortisol production (Saenger et al., 1981, 1982a,b), or immunologic alterations (Gudbrandsson et al., 1981; Koller and Brauner, 1977; Kristensen, 1978; Kristensen and Andersen, 1978). Reductions in dietary intake of calcium, copper, or iron similarly appear to increase susceptibility to lead intoxication (Mahaffey and Michaelson, 1980).

The slowly progressive chronic lead nephropathy resulting from years of relatively low-dose lead absorption observed in adults is strikingly different from the acute lead nephropathy arising from the relatively brief but intense exposure arising from childhood pica. Typical acid-fast intranuclear inclusions are, for example, far less common in the kidneys of adults (Cramer et al., 1974; Wedeen et al., 1975). Although aminoaciduria has been found to be greater in groups of lead workers than in controls (Clarkson and Kench, 1956; Goyer et al., 1972), proximal tubular dysfunction is more difficult to demonstrate in adults with chronic lead nephropathy than in acutely exposed children (Cramer et al., 1974). It should be remembered, however, that children with the Fanconi syndrome have far more severe acute lead intoxication than is usual for workmen on the job. In contrast to the reversible Fanconi syndrome associated with childhood lead poisoning, proximal tubular reabsorptive defects in occupationally exposed adults are uncommon and subtle; clearance measurements are often required to discern impaired tubular reabsorption in chronic lead nephropathy. Hyperuricemia is frequent among lead workers (Albahary et al., 1965; Garrod, 1859; Hong et al., 1980; Landrigan et al., 1982), presumably a consequence of specific lead inhibition of uric acid excretion, increased uric acid production (Emmerson et al., 1971; Granick et al., 1978; Ludwig, 1957), and prerenal azotemia from volume depletion. The hyperuricemia in adults contrasts with the reduced serum uric acid levels usually associated with the Fanconi syndrome in childhood lead poisoning. Although aminoaciduria and glycosuria are unusual in chronic lead nephropathy, Hong et al. (1980) reported a disproportionate reduction in the maximum reabsorptive rate for glucose compared with para-aminohippuric acid (PAH) in five of six lead workers they studied. PAH transport has not been consistently altered beyond that expected in renal failure of any etiology (Hong et al., 1980; Wedeen et al., 1975). Biagini et al. (1977) have, however, reported a good negative linear correlation between the one-day EDTA lead-mobilization test

and C_{pah} in 11 patients with histologic evidence of lead-induced ultrastructural abnormalities in proximal tubules.

The differences between lead nephropathy in children and adults would not appear to be a consequence of the route of exposure, since a case of pica in an adult (geophagic lead nephropathy) studied by Wedeen et al. (1978) showed the characteristics of chronic rather than acute lead nephropathy; intranuclear inclusions were absent and the GFR was reduced out of proportion to the effective renal plasma flow.

12.5.3.4 Lead and Gouty Nephropathy. Renal disease in gout can often be attributed to well defined pathogenetic mechanisms including urinary tract stones and acute hyperuricemic nephropathy with intratubular uric acid deposition (Bluestone et al., 1977). In the absence of intra- or extra-renal urinary tract obstruction, the frequency, mechanism, and even the existence of a renal disease peculiar to gout remains in question. While some investigators have described "specific" uric acid-induced histopathologic changes in both glomeruli and tubules (Gonick et al., 1965; Sommers and Churg, 1982), rigorously defined controls with comparable degrees of renal failure were not studied simultaneously. Specific histologic changes in the kidneys in gout have not been found by others (Pardo et al., 1968; Bluestone et al., 1977). Glomerulonephritis, vaguely defined "pyelonephritis" (Heptinstall, 1974), or intra- and extra-renal obstruction may have sometimes been confused with the gouty kidney, particularly in earlier studies (Fineberg and Altschul, 1956; Gibson et al., 1980b; Mayne, 1955; McQueen, 1951; Schnitker and Richter, 1936; Talbott and Terplan, 1960; Williamson, 1920).

The histopathology of interstitial nephritis in gout appears to be non-specific and cannot usually be differentiated from that of "pyelonephritis," nephrosclerosis, or lead nephropathy on morphologic grounds alone (Barlow and Beilin, 1968; Bluestone et al., 1977; Greenbaum et al., 1961; Heptinstall, 1974; Inglis et al., 1978). Indeed, renal histologic changes in non-gouty hypertensive patients have been reported to be identical to those found in gout patients (Cannon et al., 1966). In these hypertensive patients, serum uric acid levels paralleled the BUN.

Confusion between glomerular and interstitial nephritis can in part be explained by the tendency of proteinuria to increase as renal failure progresses, regardless of the underlying etiology (Batuman et al., 1981). In the absence of overt lead intoxication it may, therefore, be difficult to recognize surreptitious lead absorption as a factor contributing to renal failure in gouty patients. Further, medullary urate deposits, formerly believed to be characteristic of gout (Brown and Mallory, 1950; Mayne, 1955; McQueen, 1951; Fineberg and Altschul, 1956; Talbott and Terplan, 1960), have more recently been reported in end-stage renal disease patients with no history of gout (Cannon et al., 1966; Inglis et al., 1978; Linnane et al., 1981; Östberg, 1968; Verger et al., 1967). Whether such crystalline deposits contribute to, or are a consequence of, renal damage cannot be determined with confidence. In

the presence of severe hyperuricemia (serum uric acid greater than 20 μg/dl), intraluminal crystal deposition may produce acute renal failure because of tubular obstruction (Emmerson, 1980) associated with grossly visible medullary streaks. In chronic renal failure without gout or massive hyperuricemia, the functional significance of such medullary deposits is unclear (Linnane et al., 1981). Moreover, medullary microtophi, presumably developing around intraluminal deposits, may extend into the renal interstitium, inducing foreign body reactions with giant cell formation. Such amorphous deposits may require alcohol fixation and deGalantha staining for identification (Verger et al., 1967). Because of the acid milieu, medullary deposits are usually uric acid, while microtophi developing in the neutral pH of the renal cortex are usually monosodium urate. Both amorphous and needle-like crystals have been demonstrated in kidneys of non-gout and hyperuricemic patients frequently in association with arteriolonephrosclerosis (Inglis et al., 1978; Cannon et al., 1966; Ostberg, 1968). Urate deposits therefore, are not only not diagnostic, but may be the result, rather than the cause, of interstitial nephritis. The problem of identifying unique characteristics of the gouty kidney has been further confounded by the coexistence of pyelonephritis, diabetes mellitis, hypertension, and the aging process itself.

Although the outlook for gout patients with renal disease was formerly considered grim (Talbott, 1949; Talbott and Terplan, 1960), more recent long-term follow-up studies suggest a benign course in the absence of renovascular or other supervening disease (Fessel, 1979; Yü and Berger, 1982; Yü, 1982). Over the past four decades the reported incidence of renal disease has varied from greater than 25 percent (Fineberg and Altschul, 1956; Henck et al., 1941; Talbott, 1949; Talbott and Terplan, 1960; Wyngaarden, 1958) to less than 2 percent, as observed by Yü (1982) in 707 patients followed from 1970 to 1980. The low incidence of renal disease in some hyperuricemic populations does not support the view that elevated serum uric acid levels of the degree ordinarily encountered in gout patients is harmful to the kidneys (Emmerson, 1980; Fessel, 1979; Ramsey, 1979; Reif et al., 1981). Similarly, the failure of the xanthine oxidase inhibitor, allopurinol, to reverse the course of renal failure in gout patients despite marked reductions in the serum uric acid (Bowie et al., 1967; Levin and Abrahams, 1966; Ogryzlo et al., 1966; Rosenfeld, 1974; Wilson et al., 1967) suggests that renal disease in gout may be due in part to factors other than uric acid. Some studies have, however, suggested a possible slowing of the rate of progression of renal failure in gout by allopurinol (Gibson et al., 1978, 1980a,b; Briney et al., 1975). While the contribution of uric acid to the renal disease of gout remains controversial, the hypothesized deleterious effect of hyperuricemia on the kidney has no bearing on other potential mechanisms of renal damage in these patients.

Although hyperuricemia is universal in patients with renal failure, gout is rare in such patients except when the renal failure is due to lead. Gout occurs in approximately half of

the patients with lead nephropathy (Emmerson, 1963, 1973; Ball and Sorenson, 1969; Richet et al., 1965). Moreover, among gout patients in Scotland without known lead exposure, blood lead levels were found to be higher than in non-gouty controls (Campbell et al., 1978). The long association of lead poisoning with gout raises the possibility that lead absorption insufficient to produce overt lead intoxication may, nevertheless, cause gout with slowly progressive renal failure. Garrod (1859), Ball and Sorenson (1969), and Emmerson et al., (1971) demonstrated that lead reduces uric acid excretion, thereby creating the internal milieu in which gout can be expected. The mechanism of hyperuricemia in lead poisoning is, however, unclear. Serum uric acid levels would be expected to rise in association with lead induced pre-renal azotemia; increased proximal tubule reabsorption of uric acid could result from reduced glomerular filtration rate due to chronic volume depletion. Increased tubular reabsorption of uric acid in lead nephropathy was suggested by the pyrazinamide suppression test (Emmerson, 1971), but interpretation of this procedure has been questioned (Holmes and Kelly, 1974). Lead inhibition of tubular secretion of uric acid, therefore, remains another possible mechanism of reduced uric acid excretion. In addition, some investigators have found increased uric acid excretion in saturnine gout patients, thereby raising the possibility that lead increases uric acid production in addition to reducing uric acid excretion (Emmerson et al., 1971; Ludwig, 1957; Granick et al., 1978).

Having specifically excluded patients with gout or hypertension from their study of occupational lead nephropathy, Wedeen and collaborators examined the possible role of lead in the etiology of the gouty kidney (Batuman et al., 1981). To test the hypothesis that surreptitious lead absorption may sometimes contribute to renal failure in gout, 44 armed service veterans with gout were examined by the EDTA lead-mobilization test. Individuals currently exposed to lead (including lead workers) were specifically excluded. Collection of urine during the EDTA lead-mobilization test was extended to three days because reduced GFR delays excretion of the lead chelate (Emmerson, 1963). Note that the EDTA test does not appear to be nephrotoxic even for patients with preexisting renal failure (Wedeen et al., 1983). Half of the gout patients had normal renal function and half had renal failure as indicated by serum creatinines over 1.5 mg/dl (mean = 3.0; standard error = 0.4 mg/dl), reflecting approximately 70 percent reduction in renal function. The groups were comparable in regard to age, duration of gout, incidence of hypertension, and history of past lead exposure. The mean (and standard error) blood lead concentration was 26 (± 3) µg/dl in the patients with reduced renal function and 24 (± 3) µg/dl in the gout patients with normal kidney function. The gout patients with renal dysfunction, however, excreted significantly more lead chelate than did those without renal dysfunction (806 ± 90 and 470 ± 52 µg Pb over 3 days, respectively).

Ten control patients with comparable renal failure excreted 424 ± 72 µg lead during the 3-day EDTA test (2 g i.m.). The non-gout control patients with renal failure had normal lead

stores (Emmerson, 1973; Wedeen et al., 1975), indicating that the excessive mobilizable lead in the gout patients with renal failure was not a consequence of reduced renal function per se. These studies suggest that excessive lead absorption may sometimes be responsible for the gouty kidney in contemporary patients, as appeared to be the case in the past (Wedeen, 1981). While the EDTA lead-mobilization test cannot prove the absence of other forms of renal disease, when other known causes are excluded by appropriate diagnostic studies, a positive EDTA test can indicate that lead may be a contributing cause of renal failure.

The source of lead exposure in these armed service veterans could not be determined with confidence. A history of transient occupational exposure and occasional moonshine consumption was common among all the veterans, but the medical histories did not correlate with either the EDTA lead-mobilization test or the presence of renal failure. The relative contributions of airborne lead, industrial sources, and illicit whiskey to the excessive body lead stores demonstrated by the EDTA lead-mobilization test could not, therefore, be determined.

12.5.3.5 Lead and Hypertensive Nephrosclerosis. Hypertension is another putative complication of excessive lead absorption that has a long and controversial history. Hypertension has often been associated with lead poisoning, frequently together with renal failure (Beevers et al., 1980; Dingwall-Fordyce and Lane, 1963; Emmerson, 1963; Legge, 1901; Lorimer, 1886; Morgan, 1976; Oliver, 1891; Richet et al., 1966; Vigdortchik, 1935). However, a number of investigators have failed to find such an association (Belknap, 1936; Brieger and Rieders, 1959; Cramer and Dahlberg, 1966; Fouts and Page, 1942; Malcolm, 1971; Mayers, 1947; Ramirez-Cervantes et al., 1978). Because of the absence of both uniform definitions of excessive lead exposure and prospective control populations, the true contribution of lead to hypertension at various levels and durations of exposure is unknown. Similarly, it is not clear whether lead-induced hypertension is mediated by renal disease, vascular effects, or mechanisms involving vasoactive hormones or sodium transport. Definitive epidemiological studies remain to be performed, but the etiologic role of lead in hypertension is likely to remain clouded as long as the etiology of "essential" hypertension is unknown.

Among non-occupationally exposed individuals, hypertension and serum uric acid levels have been found to correlate with blood lead levels (Beevers et al., 1976). Moreover, the kidneys of patients with chronic lead nephropathy may show uric acid microtophi and the vascular changes of "benign essential hypertension" even in the absence of gout and hypertension (Cramer et al., 1974; Inglis et al., 1978; Morgan, 1976; Wedeen et al., 1975). In a long-term follow-up study of 624 patients with gout, Yü and Berger (1982) reported that while hyperuricemia alone had no deleterious effect on renal function, decreased renal function was more likely to occur in gout patients with hypertension and/or ischemic heart disease than in those with uncomplicated gout.

Like gout, hypertension was specifically excluded from the study of occupational lead nephropathy by Wedeen et al. (1975, 1979) in order to isolate lead-induced renal disease. Hypertension by itself is widely accepted as a cause of renal failure. Currently, however, the renal sequelae of moderate hypertension appear to be less dramatic than in the past (Kincaid-Smith, 1982). In order to determine if unsuspected excessive body lead stores might contribute to the renal disease of hypertension, 3-day EDTA (2 g i.m.) lead mobilization tests were performed in hypertensive armed service veterans with and without renal failure (Batuman et al., 1983). A significant increase in mobilizable lead was found in hypertensive subjects with renal disease compared to those without renal disease. Control patients with renal failure again demonstrated normal mobilizable lead, thereby supporting the view that renal failure is not responsible for the excess mobilizable lead in patients with hypertension and renal failure. These findings suggest that patients who would otherwise be deemed to have essential hypertension with nephrosclerosis can be shown to have underlying lead nephropathy by the EDTA lead-mobilization test when other renal causes of hypertension are excluded.

The mechanism whereby lead induces hypertension remains unclear. Although renal disease, particularly at the end-stage, is a recognized cause of hypertension, renal arteriolar histologic changes may precede both hypertension and renal disease (Wedeen et al., 1975). Lead may therefore induce hypertension by direct or indirect effects on the vascular system.

Studies of hypertension in moonshine consumers have indicated the presence of hyporeninemic hypoaldosteronism. A blunted plasma renin response to salt depletion has been described in lead poisoned patients; this response can be restored to normal by chelation therapy (McAllister et al., 1971; Gonzalez et al., 1978; Sandstead et al., 1970a). The diminished renin-aldosterone responsiveness found in moonshine drinkers could not, however, be demonstrated in occupationally exposed men with acute lead intoxication (Campbell et al., 1979). Although the impairment of the renin-aldosterone system appears to be independent of renal failure and hypertension, hyporeninemic hypoaldosteronism due to lead might contribute to the hyperkalemia (Morgan, 1976) and the exaggerated natriuresis (Fleischer et al., 1980) of some patients with "benign essential hypertension." Since urinary kallikrein excretion is reduced in lead workers with hypertension, it has been suggested that the decrease in this vasodilator may contribute to lead-induced hypertension (Boscolo et al., 1981). The specificity of kallikrein suppression in the renal and hypertensive manifestions of excessive lead absorption cannot, however, be determined from available data, because lead workers without hypertension and essential hypertensive patients without undue lead absorption also have reduced urinary kallikrein excretion.

12.5.3.6 General Population Studies. Few studies have been performed to evaluate the possible harmful effects of lead on the kidneys in populations without suspected excessive lead absorption from occupational or moonshine exposure.

An epidemiological survey in Scotland of households with water lead concentrations in excess of WHO recommendations (100 µg/l) revealed a close correlation between water lead content and blood lead and serum urea concentrations (Campbell et al., 1977). In 970 households lead concentrations in drinking water ranged from <0.1 to >8.0 mg/l. After clinical and biochemical screening of 283 subjects from 136 of the households with water lead concentrations in excess of 100 µg/l, a subsample of 57 persons with normal blood pressure and elevated serum urea (40 µg/dl) was compared with a control group of 54 persons drawn from the study group with normal blood pressure and normal serum urea. The frequency of renal dysfunction in individuals with elevated blood lead concentratons (>41 µg/dl) was significantly greater than that of age- and sex-matched controls.

Since 62 general practitioners took part in the screening, the subsamples may have come from many different areas; however, it was not indicated if matching was done for place of residence. The authors found a significantly larger number of high blood lead concentrations among the persons with elevated serum urea and claimed that elevated water lead concentration was associated with renal insufficiency as reflected by raised serum urea concentrations. This is difficult to accept since serum urea is not the method of choice for evaluating renal function. Despite reservations concerning use of the BUN for assessing renal function (described above), these findings are consistent with the view that excessive lead absorption from household water causes renal dysfunction. However, the authors used unusual statistical methods and could not exclude the reverse causal relationship, i.e., that renal failure had caused elevated blood lead levels in their study group. A carefully matched control population of azotemic individuals from low lead households would have been helpful for this purpose. A more convincing finding in another subsample was a strong association between hyperuricemia and blood lead level. This was also interpreted as a sign of renal insufficiency, but it may have represented a direct effect of lead on uric acid production or renal excretion.

These investigators have also found a statistically significant correlation between blood lead concentration and hypertension. Tap-water lead did not, however, correlate with blood lead among the hypertensive group, thus suggesting that other environmental sources of lead may account for the presence of high blood lead concentrations among hypertensive persons in Scotland (Beevers et al., 1976, 1980).

12.5.4 Mortality Data

Cooper and Gaffey (1975) analyzed mortality data available from 1267 death certificates for 7032 lead workers who had been hired by 16 smelting or battery plants between 1900 and 1969. Standardized mortality ratios revealed an excess of observed over predicted deaths from "other hypertensive disease" and "chronic nephritis and other renal sclerosis." The authors

concluded that "high levels of lead absorption such as occurred in many of the workers in this series, can be associated with chronic renal disease." Although renal carcinomas have been observed in lead poisoned rats, no increase in cancer rates was evident in this study of lead workers (Cooper, 1976; see Section 12.7). Reports of renal carcinoma among lead workers are distinctly unusual (Baker et al., 1980).

In a more limited study of 241 Australian smelter employees who were diagnosed as lead poisoned between 1928 and 1959 by a government medical board, 140 deaths were identified between 1930 and 1977 (McMichael and Johnson, 1982). Standard proportional mortality rates of the lead-exposed workers compared with 695 non-lead-exposed employees revealed an overall three-fold excess in deaths due to chronic nephritis and a two-fold excess in deaths due to cerebral hemorrhage in the lead-exposed workers. Over the 47 years of this retrospective study the number of deaths from chronic nephritis decreased from an initial level of 36 percent to 4.6 percent among the lead-exposed workers, compared with a drop from 8.7 percent to 2.2 percent among controls. From 1965 to 1977 the age-standardized mortality rates from chronic nephritis were the same for the lead-worker and control groups, although both rates were higher than the proportional mortality rate for the general population of Australian males. The latter observation indicated that the excessive deaths from chronic nephritis among lead-poisoned workers at the smelter had declined in recent decades.

Despite substantial evidence that lead produces interstitial nephritis in adults, the impact of chronic lead nephropathy on the general population is unknown. The diagnosis of lead nephropathy is rarely made in dialysis patients in the United States. The absence of the diagnosis does not, however, provide evidence for the absence of the disease. Advanced renal failure is usually encountered only many years after excessive lead exposure. Moreover, acute intoxication may never have occurred, and neither heme enzyme abnormalities nor elevated blood lead levels may be present at the time renal failure becomes apparent. The causal relationship between lead absorption and renal disease may therefore not be evident. It is likely that such cases of lead nephropathy have previously been included among other diagnostic categories such as pyelonephritis, interstitial nephritis, gouty nephropathy, and hypertensive nephrosclerosis. Increasing proteinuria as lead nephropathy progresses may also cause confusion with primary glomerulonephritis. It should also be noted that the End Stage Renal Disease Program (Health Care Financing Administration, 1982) does not even include the diagnosis of lead nephropathy in its reporting statistics, regardless of whether the diagnosis is recognized by the attending nephrologist.

12.5.5 Experimental Animal Studies of the Pathophysiology of Lead Nephropathy

12.5.5.1 Lead Uptake by the Kidney. Lead uptake by the kidney has been studied in vivo and in vitro using renal slices. Vander et al. (1977) performed renal clearance studies in dogs

two hours after a single i.v. dose of 0.1 or 0.5 mg lead acetate containing 1-3 mCi of ^{203}Pb or 1 hour after continous i.v. infusion of 0.1-0.15 mg/kg-hour. These investigators reported that 43-44 percent of the plasma lead was ultrafiltrable, with kidney reabsorption values of 89-94 percent for the ultrafiltrable fraction. A subsequent stop-flow analysis investigation by Victery et al. (1979a), using dogs given a single i.v. dose of lead acetate at 0.2 or 10.0 mg/kg, showed both proximal and distal tubular reabsorption sites for lead. Distal reabsorption was not linked to sodium chloride or calcium transport pathways. Proximal tubule reabsorption was demonstrated in all animals tested during citrate or bicarbonate infusion. Another experiment (Victery et al., 1979b) examined the influence of acid-base status on renal accumulation and excretion of lead in dogs given 0.5-50 µg/kg hr as an infusion or in rats given access to drinking water containing 500 ppm Pb for 2-3 months. These showed that alkalosis increased lead entry into tubule cells via both luminal and basolateral membranes, with a resultant increase in both renal tissue accumulation and urinary excretion of lead. Similarly, acutely induced alkalosis increased lead excretion in rats previously given access to drinking water containing 500 ppm lead for 2-3 months. These authors also concluded that the previously reported acute exposure experiments concerning the renal handling of lead were at least qualitatively similar to results of the chronic exposure experiments and that rats were an acceptable model for investigating the effects of alkalosis on the excretion of lead following chronic exposure.

In vitro studies (Vander et al., 1979) using slices of rabbit kidney incubated with ^{203}Pb acetate at lead concentrations of 0.1 or 1.0 µM over 180-minute time intervals showed that a steady-state uptake of ^{203}Pb by slices (ratio of slice: medium uptake in the range of 10-42) was reached after 90 minutes and that lead could enter the slices as a free ion. Tissue slice uptake was reduced by a number of metabolic inhibitors, thus suggesting a possible active transport mechanism. Tin (Sn IV) was found to markedly reduce ^{203}Pb uptake into the slices but not to affect lead efflux or para-aminohippurate accumulation. This finding raises the possibility that Pb and Sn (IV) compete for a common carrier.

Subsequent studies also using rabbit kidney slices (Vander and Johnson, 1981) showed that co-transport of ^{203}Pb into the slices in the presence of organic anions such as cysteine, citrate, glutathione, histidine, or serum ultrafiltrate was relatively small compared with uptake due to ionic lead.

In summary, it is clear from the above in vivo and in vitro studies on several different animal species that renal accumulation of lead is an efficient process that occurs in both proximal and distal portions of the nephron and at both luminal and basolateral membranes. The transmembrane movement of lead appears to be mediated by an uptake process that is subject to inhibition by several metabolic inhibitors and the acid-base status of the organism.

12.5.5.2 Intracellular Binding of Lead in the Kidney. The bioavailability of lead inside renal tubule cells under low or ^{203}Pb tracer exposure conditions is mediated in part by binding to several high affinity cytosolic binding proteins (Oskarsson et al., 1982; Mistry et al., 1982) and, at higher exposure conditions, by the formation of cytoplasmic and intranuclear inclusion bodies (Goyer et al., 1970a). These inclusion bodies have been shown by both cell fractionation (Goyer et al., 1970a) and X-ray microanalysis (Fowler et al., 1980) to contain the highest intracellular concentrations of lead. Saturation analysis of the renal 63,000 dalton (63K) cytosolic binding protein has shown that it possesses an approximate dissociation constant (K_d) of 10^{-8} M (Mistry et al., 1982). These data quantify the high affinity nature of this protein for lead and explain the previously reported finding (Oskarsson et al., 1982) that this protein constitutes a major intracellular lead-binding site in the kidney cytosol. Biochemical studies on the protein components of isolated rat kidney intranuclear inclusion bodies have shown that the main component has an approximate molecular weight of 27K (Moore et al., 1973) or 32K (Shelton and Egle, 1982) and that it is rich in the dicarboxylic amino acids glutamate and aspartate (Moore et al., 1973). The isoelectric point of the main nuclear inclusion body protein has been reported to be pI = 6.3 and appeared from two-dimensional gel analysis to be unique to nuclei of lead-injected rats (Shelton and Egle, 1982). The importance of the inclusion bodies resides with the suggestion (Goyer et al., 1970a; Moore et al., 1973; Goyer and Rhyne, 1973) that, since these structures contain the highest intracellular concentrations of lead in the kidney proximal tubule and hence account for much of the total cellular lead burden, they sequester lead to some degree away from sensitive renal organelles or metabolic (e.g., heme biosynthetic) pathways until their capacity is exceeded. The same argument would apply to the high affinity cytosolic lead-binding proteins at lead exposure levels below those that cause formation of inclusion bodies. It is currently unclear whether lead-binding to these proteins is an initial step in the formation of the cytoplasmic or nuclear inclusion bodies (Oskarsson et al., 1982).

12.5.5.3 Pathological Features of Lead Nephropathy. The main morphological effects of lead in the kidney are manifested in renal proximal tubule cells and interstitial spaces between the tubules. A summary of morphological findings from some recent studies involving a number of animal species is given in Table 12-10. In all but one of these studies, formation of intranuclear inclusion bodies is a common pathognomic feature for all species examined. In addition, proximal tubule cell cytomegaly and swollen mitochondria with increased numbers of lysosomes were also observed in two of the chronic exposure studies (Fowler et al., 1980; Spit et al., 1981). Another feature reported in three of these studies (Hass et al., 1964; White, 1977; Fowler et al., 1980) was the primary localization of morphological changes in the straight (S_3) segments of the proximal tubule, thereby indicating that not all cell types of

TABLE 12-10. MORPHOLOGICAL FEATURES OF LEAD NEPHROPATHY IN VARIOUS SPECIES

Species	Pb dose regimen	Morphological findings: Nuclear inclusions	Increased mitochondrial swelling	Increased lysosomes	Interstitial fibrosis	Reference
Rabbit	0.5% Pb acetate in diet for up to 55 weeks	+	----------ND----------		+	Hass et al., 1964
Rat	1% Pb in d.w. for 9 weeks	+	+	ND	+	Goyer, 1971
Dog	50 µg Pb/kg for 5 weeks*	+	----------ND----------		ND	White, 1977
Monkey	0, 1.5, 6.0, 15 µg Pb/day** 6 days/week for 9 months	+	----------ND----------		ND	Colle et al., 1980
Rat	0, 0.5, 5, 25, 50, 250 ppm Pb**	+	+	--	--	Fowler et al., 1980
Rabbit	0, 0.25, 0.50 µg Pb/kg*** 3 days/wk for 14 weeks	--	--	+	--	Spit et al., 1981
Ringed dove	100 µg Pb/ml**	+	+	--	--	Kendall et al., 1981

* Dosed by oral gavage

** Drinking water ad libitum

***Subcutaneous injection

ND - Not determined

the kidney are equally involved in the toxicity of lead to this organ. Interstitial fibrosis has also been reported in rabbits (Hass et al., 1964) given diets containing 0.5 percent lead acetate for up to 55 weeks and in rats (Goyer, 1971) given drinking water containing lead acetate for 9 weeks.

12.5.5.4 Functional Studies.

12.5.5.4.1 Renal blood flow and glomerular filtration rate. Studies by Aviv et al. (1980) concerning the impact of lead on renal function as assessed by renal blood flow (RBF) and glomerular filtration rate (GFR) have reported significant ($p < 0.01$) reductions in both of these parameters in rats at 3 and 16 weeks after termination of exposure to 1 percent lead acetate in drinking water. Statistically significant ($p < 0.05$) reduction of GFR has also been recently described (Victery et al., 1981) in dogs 2.5-4 hours after a single i.v. dose of 3.0 mg Pb/kg. In contrast, studies by others (Johnson and Kleinman, 1979; Hammond et al., 1982) were not able to demonstrate reduction in GFR or RBF using the rat as a model. The reasons behind these reported differences are presently unclear but may be related to differences in experimental design, age, or other variables.

12.5.5.4.2 Tubular function. Exposure to lead has also been reported to produce tubular dysfunction (Studnitz and Haeger-Aronsen, 1962; Goyer, 1971; Mouw et al., 1978; Suketa et al., 1979; Victery et al., 1981, 1982a,b, 1983). An early study (Studnitz and Haeger-Aronsen, 1962) reported aminoaciduria in rabbits given a single dose of lead at 125 mg/kg, with urine collected over a 15-hour period. Goyer et al. (1970b) described aminoaciduria in rats following exposure to 1 percent lead acetate in the diet for 10 weeks. Wapnir et al. (1979) confirmed a mild hyperaminoaciduria in rats injected with lead at 20 mg/kg five times a week for six weeks but found no changes in urinary excretion of phosphate or glucose.

Other studies (Mouw et al., 1978; Suketa et al., 1979; Victery et al., 1981, 1982a,b, 1983) have focused attention on increased urinary excretion of electrolytes. Mouw et al. (1978) reported increased urinary excretion of sodium, potassium, calcium, and water in dogs given a single i.v. injection of lead at 0.6 or 3.0 mg/kg over a 4-hour period despite a constant GFR, indicating decreased tubular reabsorption of these substances. Suketa et al. (1979) treated rats with a single oral dose of lead at 0, 5, 50, or 200 mg/kg and killed the animals at 0, 6, 12, or 24 hours after treatment. A dose-related increase in urinary sodium, potassium, and water was observed over time. Victery et al. (1981, 1982a,b, 1983) studied zinc excretion in dogs over a 4-hour period following an i.v. injection of lead at 0.3 or 3.0 mg/kg. These investigators reported maximal increases in zinc excretion of 140 ng/min at the 0.3 mg/kg dose and 300 ng/min at the 3.0 mg/kg dose at the end of the 4-hour period. In contrast, in studies by Mouw et al. (1978) no changes in urinary excretion of sodium or potassium were noted. Urinary protein or magnesium excretion were also unchanged.

The results of the above studies indicate that acute or chronic lead treatment is capable of producing tubular dysfunction in several species of animals, as manifested by increased urinary excretion of amino acid nitrogen and some ions such as Zn^{2+}, Ca^{2+}, Na^{+}, K^{+}, and water.

12.5.6 Experimental Studies of the Biochemical Aspects of Lead Nephrotoxicity

12.5.6.1 Membrane Marker Enzymes and Transport Functions. The biochemical effects of lead in the kidney appear to be preferentially localized in the cell membranes and mitochondrial and nuclear compartments following either acute or chronic lead exposure regimens.

Oral exposure of rats to lead acetate in the diet at concentrations of 1-2 percent for 10-40 weeks was found to produce no significant changes in renal slice water content or in accumulation of paraminohippurate (PAH) or tetraethyl-ammonium (TEA). However, tissue glucose synthesis at 40 weeks and pyruvate metabolism were both significantly ($p < 0.05$) reduced (Hirsch, 1973).

Wapnir et al. (1979) examined biochemical effects in kidneys of rats injected with lead acetate (20 mg/kg) five days per week for six weeks. They observed a significant ($p < 0.05$) reduction in renal alkaline phosphatase activity and an increase in (Mg^{2+})-ATPase, but no significant changes in (Na^{+},K^{+})-ATPase, glucose-6-phosphatase, fructose 1-6 diphosphatase, tryptophan hydroxylase, or succinic dehydrogenase. These findings indicated that preferential effects occurred only in marker enzymes localized in the brush border membrane and mitochondrial inner membrane. Suketa et al. (1979) reported marked (50-90 percent) decreases in renal (Na^{+},K^{+})-ATPase at 6-24 hours following a single oral administration of lead acetate at a dose of 200 mg/kg. A later study (Suketa et al., 1981) using this regi-men showed marked decreases in renal (Na^{+}, K^{+})-ATPase but no significant changes in (Mg^{2+})-ATPase after 24 hours, thus indicating inhibition of a cell membrane marker enzyme prior to changes in a mitochondrial marker enzyme.

12.5.6.2 Mitochondrial Respiration/Energy-Linked Transformation. Effects of lead on renal mitochondrial structure and function have been studied by a number of investigators (Goyer, 1968; Goyer and Krall, 1969a,b; Fowler et al., 1980, 1981a,b). Examination of proximal tubule cells of rats exposed to drinking water containing 0.5-1.0 percent lead acetate for 10 weeks (Goyer, 1968; Goyer and Krall, 1969a,b) or 250 ppm lead acetate for 9 months (Fowler et al., 1980) has shown swollen proximal tubule cell mitochondria *in situ*. Common biochemical findings in these studies were decreases in respiratory control ratios (RCR) and inhibition of state-3 respiration, which was most marked for NAD-linked substrates such as pyruvate/malate. Goyer and Krall (1969a,b) found these respiratory effects to be associated with a decreased capacity of mitochondria to undergo energy-linked structural transformation.

In vitro studies (Garcia-Cañero et al., 1981) using 10^{-4} M lead demonstrated decreased renal mitochondrial membrane transport of pyruvate or glutamate associated with decreased res-

piration for these two substrates. Other in vitro studies (Fowler et al., 1981a,b) have shown decreased renal mitochondrial membrane energization as measured by the fluorescent probes 1-anilino,-8 napthalenesulfonic acid (ANS) or ethidium bromide following exposure to lead acetate at concentrations of 10^{-5} to 10^{-3} M lead. High amplitude mitochondrial swelling was also observed by light scattering.

The results of the above studies indicate that lead produces mitochondrial swelling both in situ and in vitro, associated with a decrease in respiratory function that is most marked for RCR and state-3 respiration values. The structural and respiratory changes appear to be linked to lead-induced alteration of mitochondrial membrane energization.

12.5.6.3 Renal Heme Biosynthesis. There are several reports concerning the effects of lead on renal heme biosynthesis following acute or chronic exposure. Silbergeld et al. (1982) injected rats with lead at 10 μM/kg per day for three days and examined effects on several tissues including kidney. These investigators found an increase in δ-aminolevulinic acid synthetase (ALA-S) following acute injection and no change following chronic exposure (first indirectly via their dams' drinking water containing lead at 10 mg/ml until 30 days of age and then directly via this drinking water to 40-60 days of age). Renal tissue content of δ-aminolevulinic acid (ALA) was increased in both acutely and chronically exposed rats. Renal δ-aminolevulinic acid dehydrase (ALA-D) was found to be inhibited in both acute and chronic treatment groups. Gibson and Goldberg (1970) injected rabbits s.c. with lead acetate at doses of 0, 10, 30, 150, or 200 mg Pb/week for up to 24 weeks. The mitochondrial enzyme ALA-S in kidney was found to show no measurable differences from control levels. Renal ALA-D, which is found in the cytosol fraction, showed no differences from control levels when glutathione was present but was significantly reduced ($p < 0.05$) to 50 percent of control values for the pooled lead-treated groups when glutathione was absent. Mitochondrial heme synthetase (ferrochelatase) was not significantly decreased in lead-treated versus control rabbits, but this enzyme in the kidney was inhibited by 72 and 94 percent at lead-acetate concentrations of 10^{-4} and 10^{-3} M lead, respectively. Accumulation (12-15 fold) of both ALA and porphobilinogen (PBG) was also observed in kidney tissue of lead-treated rabbits relative to controls. Zawirska and Medraś (1972) injected rats with lead acetate at a dose of 3 mg Pb/day for up to 60 days and noted a similar renal tissue accumulation of uroporphyrin, coproporphyrin, and protoporphyrin. A study by Fowler et al. (1980) using rats exposed through 9 months of age to 50 or 250 ppm lead acetate in drinking water showed significant inhibition of the mitochondrial enzymes ALA-S and ferrochelatase but no change in the activity of the cytosolic enzyme ALA-D. Similar findings have been reported for ALA-D following acute i.p. injection of lead acetate at doses of 5-100 mg Pb/kg at 16 hours prior to sacrifice (Woods and Fowler, 1982). In the latter two studies, reduced glutathione was present in the assay mixture.

To summarize the above studies (also see Table 12-11), the pattern of alteration of renal heme biosynthesis by lead is somewhat different from that usually observed with this agent in other tissues (see Section 12.3). A general lack of lead-induced inhibition of renal ALA-D is one frequently reported observation in this tissue except under conditions of high-level exposure. Such a finding could result from the presence of the recently described high affinity cytosolic lead-binding proteins (Oskarsson et al., 1982; Mistry et al., 1982) in the kidney and/or the formation of lead-containing intranuclear inclusion bodies in this tissue (Goyer, 1971; Fowler et al., 1980), which would sequester most of the intracellular lead away from other organelle compartments until the capacity of these mechanisms is exceeded. Based on the observations of Gibson and Goldberg (1970), tissue or assay concentrations of glutathione may also be of importance to the effects of lead on this enzyme. The observed lack of ALA-S induction in kidney mitochondria reported in the above studies may have been caused by decreased mitochondrial protein synthesis capacity or, as previously suggested (Fowler et al., 1980), by overwhelming inhibition of this enzyme by lead, such that any inductive effects were not measurable. Further research is needed to resolve these questions.

12.5.6.4 Lead Alteration of Renal Nucleic Acid/Protein Synthesis. A number of studies have shown marked increases in renal nucleic acid or protein synthesis following acute or chronic exposure to Pb acetate. One study (Choie and Richter, 1972a) conducted on rats given a single intraperitoneal injection of lead acetate showed an increase in ^{3}H-thymidine incorporation. A subsequent study (Choie and Richter, 1972b) involved rats given intraperitoneal injections of 1-7 mg lead once per week over a 6-month period. Autoradiography of ^{3}H-thymidine incorporation into tubule cell nuclei showed a 15-fold increase in proliferative activity in the lead-treated rats relative to controls. The proliferative response involved cells both with and without intranuclear inclusions. Follow-up autoradiographic studies in rats given three intraperitoneal injections of lead acetate (0.05 mg Pb/kg) 48 hours apart showed a 40-fold increase in ^{3}H-thymidine incorporation 20 hours after the first lead dose and 6 hours after the second and third doses.

Choie and Richter (1974a) also studied mice given a single intracardiac injection of lead (5 µg Pb/g) and demonstrated a 45-fold maximal increase in DNA synthesis in proximal tubule cells as judged by ^{3}H-thymidine autoradiography 33 hours later. This increase in DNA synthesis was preceded by a general increase in both RNA and protein synthesis (Choie and Richter, 1974b). The above findings were essentially confirmed with respect to lead-induced increases in nucleic acid synthesis by Cihák and Seifertová (1976), who found a 13-fold increase in ^{3}H-thymidine incorporation into kidney nuclei of mice 4 hours after an intracardiac injection (5 µg Pb/g) of lead acetate. This finding was associated with a 34-fold increase in the mitotic index but no change in the activities of thymidine kinase or thymide monophosphate kinase. Stevenson et al. (1977) have also reported a 2-fold increase in ^{3}H-thymidine or

TABLE 12-11. EFFECTS OF LEAD EXPOSURE ON RENAL HEME BIOSYNTHESIS

Species	Pb dose regimen	ALA-S	ALA-D	FC*	Renal tissue porphyrins	Reference
Rabbit	10, 30, 150, 200 mg Pb/kg/wk (s.c.)	NC**	±↓	NC	↑ ALA, PBG (12-15 x)	Gibson and Goldberg, 1970
Rat	3 mg Pb/day (s.c.)	NM***	NM	NM	↑ uro-, copro-, proto-porphyrins	Zawirska and Medraś, 1972
Rat	10, 100, 1000, 5000 ppm Pb in d.w. for 3 wks	NM	↓	NM	↑ at 1000 and 5000 ppm ↑ ALA-urine	Buchet et al., 1976
Rat (dams)	10 ppm in d.w. during: 3 wks before mating 3 wks of pregnancy 3 wks after delivery	NM	NC	NM	NC	Hubermont et al., 1976
(newborns)		NM	NC	NM	↑	
Rat (dams)	100 ppm Pb in d.w. for 3 wks	NM	NC	NM	NC	Roels et al., 1977
(suckling)		NM	±↓	NM	↑	
Rat	0.5, 5, 25, 50, 250 ppm Pb in d.w. for 9 months	↓	NC	↓	NM	Fowler et al., 1980
Rat	5, 25, 50, 100 mg Pb/kg (i.p.) 16 hrs. prior to sacrifice	NM	NC	NM	NM	Woods and Fowler, 1982
Rat	10 μM Pb/kg/3 day (i.p.)	↑	↓	NM	↑ALA	Silbergeld et al., 1982
	10 mg Pb/ml in d.w. for 10-30 days	NC	↓	NM	↑ALA	

*FC - Ferro chelatase **NC - Not changed relative to controls ***NM - Not measured

^{14}C-orotic acid incorporation into kidney DNA or RNA of rats given a single intraperitoneal injection of lead chloride three days earlier.

The above studies clearly demonstrate that acute or chronic administration of lead by injection stimulates renal nucleic acid and protein synthesis in kidneys of rats and mice. The relationship between this proliferative response and formation of intranuclear inclusion bodies is currently unknown; nor is the basic mechanism underlying this response and the formation of renal adenomas in rats and mice following chronic lead exposure understood.

12.5.6.5 Lead Effects on the Renin-Angiotension System. A study by Mouw et al. (1978) used dogs given a single intravenous injection of lead acetate at doses of 0.6 or 3.0 mg Pb/kg and observed over a 4-hour period. Subjects showed a small but significant decrease in plasma renin activity (PRA) at 1 hour, followed by a large and significant ($p < 0.05$) increase from 2.5 to 4.0 hours. Follow-up work (Goldman et al., 1981) using dogs given a single intravenous injection of lead acetate at 3.0 mg Pb/kg showed changes in the renin-angiotensin system over a 3-hour period. The data demonstrated an increase in PRA, but increased renin secretion occurred in only three of nine animals. Hepatic extraction of renin was virtually eliminated in all animals, thus providing an explanation for the increased blood levels of renin. Despite the large observed increases in PRA, blood levels of angiotensin II (AII) did not increase after lead treatment. This suggests that lead inhibited the AII converting enzyme.

Exposure of rats to drinking water containing 0.5 mg Pb/ml for three weeks to five months (Fleischer et al., 1980) produced an elevation of PRA after six weeks of exposure in those rats on a sodium-free diet. No change in plasma renin substrate (PRS) was observed. At five months, PRA was significantly higher in the lead-treated group on a 1-percent sodium chloride diet, but the previous difference in renin levels between animals on an extremely low-sodium (1 meq) vs. 1-percent sodium diet had disappeared. The lead-treated animals had a reduced ability to decrease sodium excretion following removal of sodium from the diet.

Victery et al. (1982a) exposed rats to lead in utero and to drinking water solution containing 0, 100, or 500 ppm lead as lead acetate for six months. Male rats on the 100 ppm lead dose became significantly hypertensive at 3.5 months and remained in that state until termination of the experiment at six months. All female rats remained normotensive as did males at the 500-ppm dose level. PRA was found to be significantly reduced in the 100-ppm treatment males and normal in the 500-ppm treatment groups of both males and females. Dose-dependent decreases in AII/PRA ratios and renal renin content were also observed. Pulmonary AII converting enzyme was not significantly altered. It was concluded that, since the observed hypertension in the 100-ppm group of males was actually associated with reduction of PRA and AII, the renin-angiotensin system was probably not directly involved in this effect.

Webb et al. (1981) examined the vascular responsiveness of helical strips of tail arteries in rats exposed to drinking water containing 100 ppm lead for seven months. These

investigators found that the mild hypertension associated with this regimen was associated with increased vascular responsiveness to α-adrenergic agonists.

Male rats exposed to lead in utero and prior to weaning indirectly by their dams' drinking water containing 0, 5, or 25 ppm lead as lead acetate, followed by direct exposure at the same levels for five months (Victery et al., 1982b), showed no change in systolic blood pressure. Rats exposed to the 25 ppm dose showed a significant ($p < 0.05$) decrease in basal PRA. Stimulation of renin release by administration of polyethylene glycol showed a significant increase in PRA but low AII values. These yielded a significant ($p < 0.001$) decrease in the AII/PRA ratio. Basal renal renin concentrations were found to be significantly reduced in both the 5 ppm ($p < 0.05$) and 25 ppm ($p < 0.01$) dose groups relative to controls.

Victery et al. (1983) exposed rats in utero to lead by maternal administration of 0, 5, 25, 100, or 500 ppm lead as lead acetate. The animals were continued on their respective dose levels through one month of age. All exposure groups had PRA values significantly ($p < 0.05$) elevated relative to controls. Renal renin concentration was found to be similar to controls in the 5 and 25 ppm groups but significantly increased ($p < 0.05$) in the 100 and 500 ppm groups. The plasma AII/PRA ratio was similar to controls in the 100 ppm group but was significantly reduced ($p < 0.05$) in the 500 ppm group.

It appears from the above studies that lead exposure at even low dose levels is capable of producing marked changes in the renin-angiotension system and that the direction and magnitude of these changes is mediated by a number of factors, including dose level, age, and sex of the species tested, as well as dietary sodium content. Lead also appears capable of directly altering vascular responsiveness to α-adrenergic agents. The mild hypertension observed with chronic low level lead exposure appears to stem in part from this effect and not from changes in the renin-angiotensin system. (See also Section 12.9.1 for a discussion of other work on the hypertensive effects of lead.)

12.5.6.6 Lead Effects on Uric Acid Metabolism. A report by Mahaffey et al. (1981) on rats exposed concurrently to lead, cadmium, and arsenic alone or in combination found significantly ($p < 0.05$) increased serum concentrations of uric acid in the lead-only group. While the biochemical mechanism of this effect is not clear, these data support certain observations in humans concerning hyperuricemia as a result of lead exposure (see Section 12.5.3) and, also, confirm an earlier report by Goyer (1971) showing increased serum uric acid concentration in rats exposed to 1 percent lead acetate in drinking water for 84 weeks.

12.5.6.7 Lead Effects on Kidney Vitamin D Metabolism. Smith et al. (1981) fed rats vitamin D-deficient diets containing either low or normal calcium or phosphate for two weeks. The animals were subsequently given the same diets supplemented with 0.82 percent lead as lead acetate. Ingestion of lead at this dose level significantly reduced plasma levels of 1,25 dihydrocholecalciferol in cholecalciferol-treated rats and in rats fed either a low phospho-

rous or low calcium diet while it had no effect in rats fed either a high calcium or normal phosphorous diet. These data suggest decreased production of 1,25-dihydrocholecalciferol in the kidney in response to lead exposure in concert with dietary deficiencies.

12.5.7 General Summary: Comparison of Lead Effects in Kidneys of Humans and Animal Models

It seems clear from the preceding review that, in general, results of experimental animal studies have confirmed findings reported for human kidney function in individuals exposed to lead for prolonged time periods and that these studies have helped illuminate the mechanisms underlying such effects. Similar morphological changes are found in kidneys of humans and animals following chronic lead exposure, including nuclear inclusion bodies, cytomegaly, swollen mitochondria, interstitial fibrosis, and increased numbers of iron-containing lysosomes in proximal tubule cells. Physiological renal changes observed in humans have also been confirmed in animal model systems in regard to increased excretion of amino acids and elevated serum urea nitrogen and uric acid concentrations. The inhibitory effects of lead exposure on renal blood flow and glomerular filtration rate are currently less clear in experimental model systems; further research is needed to clarify the effects of lead on these functional parameters in animals. Similarly, while lead-induced perturbation of the renin-angiotensin system has been demonstrated in experimental animal models, further research is needed to clarify the exact relationships among lead exposure (particularly chronic low-level exposure), alteration of the renin-angiotensin system, and hypertension in both humans and animals.

On the biochemical level, it appears that lead exposure produces changes at a number of sites. Inhibition of membrane marker enzymes, decreased mitochondrial respiratory function/cellular energy production, inhibition of renal heme biosynthesis, and altered nucleic acid synthesis are the most marked changes thus far reported. The extent to which these mitochondrial alterations occur is probably mediated in part by the intracellular bioavailability of lead, which is determined by its binding to high affinity kidney cytosolic binding proteins and deposition within intranuclear inclusion bodies.

Recent studies in humans have indicated that the EDTA lead-mobilization test is the most reliable technique for detecting persons at risk for chronic nephropathy. Blood lead measurements are a less satisfactory indicator because they may not accurately reflect cumulative absorption some time after exposure to lead has terminated.

12.6 EFFECTS OF LEAD ON REPRODUCTION AND DEVELOPMENT

Data from human and animal studies indicate that lead may exert gametotoxic, embryotoxic, and (according to animal studies) teratogenic effects that could influence the survival and development of the fetus and newborn. It appears that prenatal viability and development may also be affected by lead indirectly, via effects on various health parameters of the expectant mother. The vulnerability of the conceptus to such effects of lead has contributed to concern that the unborn may constitute a group at risk for lead health effects. Also, certain information regarding lead effects on male reproductive functions has led to concern regarding the impact of lead on men.

12.6.1 Human Studies

12.6.1.1 Historical Evidence. Findings suggesting that lead exerts adverse effects on human reproductive functions have existed in the literature since before the turn of the century. For example, Paul (1860) observed that severely lead-poisoned pregnant women were likely to abort, while those less severely intoxicated were more likely to deliver stillborn infants. Legge (1901), in summarizing the reports of 11 English factory inspectors, found that of 212 pregnancies in 77 female lead workers, only 61 viable children were produced. Fifteen workers never became pregnant; 21 stillbirths and 90 miscarriages occurred. Of 101 children born, 40 died in the first year. Legge also noted that when lead was fed to pregnant animals, they typically aborted. He concluded that maternal exposure to lead resulted in a direct action of the element on the fetus.

Four years later, Hall and Cantab (1905) discussed the increasing use of lead in nostrums sold as abortifacients in Britain. Nine previous reports of the use of diachylon ("lead plaster") in attempts to cause miscarriage were cited and 30 further cases of known or apparent use of lead in attempts to terminate real or suspected pregnancy listed. Of 22 cases described in detail, 12 resulted in miscarriage and all 12 exhibited marked signs of plumbism, including a blue gum line (in eight cases the women were known to have attempted to induce abortion). Hall's report was soon followed by those of Cadman (1905) and Eales (1905), who described three more women who miscarried following consumption of lead-containing pills.

Oliver (1911) then published statistics on the effect of lead on pregnancy in Britain (Table 12-12). These figures showed that the miscarriage rate was elevated among women employed in industries in which they were exposed to lead. Lead compounds were said by Taussig (1936) to be known for their embryotoxic properties and their use to induce abortion.

In a more recent study by Lane (1949), women exposed to lead levels of 750 $\mu g/m^3$ were examined for effects on reproduction. Longitudinal data on 15 pregnancies indicated an increase in the number of stillbirths and abortions. No data were given on urinary lead in women, but men in this sample had urinary levels of 75 to 100 µg/liter.

TABLE 12-12. STATISTICS ON THE EFFECT OF LEAD ON PREGNANCY

Sample	Number of abortions and stillbirths per 1000 females	Number of neonatal deaths (first year) per 1000 females
Housewives	43.2	150
Female workers (mill work)	47.6	214
Females exposed to lead premaritally	86.0	157
Females exposed to lead after marriage	133.5	271

Source: Oliver (1911).

The above studies clearly demonstrate an adverse effect of lead at high levels on human reproductive functions, and include evidence of increased incidence of miscarriages and stillbirths when women are exposed to lead during pregnancy. The mechanisms underlying these effects are unknown at this time. Many factors could contribute to such results, ranging from lead effects on maternal nutrition or hormonal state before or during pregnancy to more direct gametotoxic, embryotoxic, fetotoxic, or teratogenic effects that could affect parental fertility or offspring viability during gestation. Pregnancy is a stress that may place a woman at higher risk for toxic lead exposure. Both iron deficiency and calcium deficiency increase susceptibility to lead, and women have an increased risk of both deficiencies during pregnancy and postpartum (Rom, 1976).

Such studies as those of Legge, Hall, and Oliver suffer from methodological inadequacies. They must be mentioned, however, because they provide evidence that effects of lead on reproduction occurred at times when women were exposed to high levels of lead. Nevertheless, evidence for adverse reproductive outcomes in women with obvious lead poisoning is of little help in defining the effects of lead at significantly lower exposure levels. Efforts have been made to define more precisely the points at which lead may affect reproductive functions in both the human female and male, as well as in animals, as reviewed below.

12.6.1.2 Effects of Lead Exposure on Reproduction.

12.6.1.2.1 Effects associated with exposure of women to lead. Since the time of the above reports, women have been largely, though not entirely (Khera et al., 1980), excluded from occupational exposure to lead; and lead is no longer used to induce abortion. Thus, little new information is available on reproductive effects of chronic exposure of women to lead. Various reports (Pearl and Boxt, 1980; Qazi et al., 1980; Timpo et al., 1979; Singh et al., 1978; Angle and McIntire, 1964) suggest that relatively high prenatal lead exposures do not invariably result in abortion or in major problems readily detectable in the first few years of life

These findings are based on only a few case histories, however, and are obviously not an adequate sample. The data are confounded by numerous variables, and longer follow-ups are needed.

In a sample population exposed to lead and to other toxic agents (including arsenic and sulfur dioxide) from the Rönnskär smelter, Nordström et al. (1978b) found an increased frequency of spontaneous abortions among women living closest to the smelter. In addition to the exposure to multiple environmental toxins, however, the study was confounded by failure to match exposed and control populations for socioeconomic status. A further study by the same authors (Nordström et al., 1979a) determined that female smelter workers at the Rönnskär smelter had an increased frequency of spontaneous miscarriage when the mother was employed by the smelter during pregnancy or had been so employed prior to pregnancy and still lived near the smelter. Also, women who worked in more highly polluted areas of the smelter were more likely to have aborted than were other employees. This report, however, suffers from the same deficiencies as the earlier study.

In regard to potential lead effects on ovarian function in human females, Panova (1972) reported a study of 140 women working in a printing plant for less than one year (1 to 12 months) where ambient air levels were <7 μg Pb/m^3. Using a classification of various age groups (20-25, 26-35, and 36-40 yr) and type of ovarian cycle (normal, anovular, and disturbed lutein phase), Panova claimed that statistically significant differences existed between the lead-exposed and control groups in the age range 20 to 25 years. Panova's report, however, does not show the age distribution, the level of significance, or data on the specificity of her method for classification. Zielhuis and Wibowo (1976), in a critical review of the above study, concluded that the study design and presentation of data were such that it is difficult to evaluate the author's conclusions. It should also be noted that no consideration was given to the dust levels of lead, an important factor in print shops.

Unfortunately, little else besides the above study appears to exist in regard to assessing the effects of lead on human ovarian function or other factors affecting female fertility. Studies offering firm data on maternal variables, e.g., hormonal state, that are known to affect the ability of the pregnant woman to carry the fetus full term are also lacking.

12.6.1.2.2 Effects associated with exposure of men to lead. Lead-induced effects on male reproductive functions have been reported in several instances. Among the earliest of these was the review of Stöfen (1974), who described data from the work of Neskov in the USSR involving 66 workers exposed chiefly to lead-containing gasoline (organic lead). In 58 men there was a decrease or disappearance of erection, in 41 there was early ejaculation, and in 44 there were a diminished number of spermatocytes. These results were confounded, however, by the presence of the other constituents of gasoline.

Lancranjan et al. (1975) reported lead-related interference with male reproductive functions. A group of 150 workmen who had long-term exposure to lead in varying degrees was studied. Clinical and toxicological criteria were used to categorize the men into four groups: lead-poisoned workmen (mean blood lead level = 74.5 µg/dl) and those showing moderate (52.8 µg/dl), slight (41 µg/dl), or "physiologic" (23 µg/dl) exposure to lead. Moderately increased lead absorption (52.8 µg/dl) was said to result in gonadal impairment. The effects on the testes were believed to be direct, in that tests for impaired hypothalamopituitary influence were negative. Also, semen analysis revealed asthenospermia and hypospermia in all groups except those with "physiologic" absorption levels, and increased teratospermia was seen in the two highest lead exposure groups.

An apparently exposure-related increase in erectile dysfunction was also found by Lancranjan et al. (1975). Problems with ejaculation and libido were said to be more common in the lead exposed groups, but their incidences did not seem to be dose-dependent. Control incidences of these difficulties were invariably lower than those of the lead exposed groups, however, so the lack of a clear cut dose-response relationship may have merely been due to inappropriate assignment of individuals to the high, moderate, and low exposure groups.

The Lancranjan et al. (1975) study has been criticized by Zielhuis and Wibowo (1976), who stated that the distributions of blood lead levels appeared to be skewed and that exposure groups overlapped in terms of lead intake. Thus, the means for each putative exposure group may not have been representative of the individuals within a group. It is difficult to discern, however, if the men were improperly assigned to exposure level groups, as blood lead levels may have varied considerably on a short term basis. Zielhuis and Wibowo also stated that the measured urinary ALA levels were unrealistically high for individuals with the stated blood lead levels. This suggests that if the ALA values were correct, the blood lead levels may have been underestimated. Other deficiencies include failure to use matched controls and exclusion of different proportions of individuals per exposure group for the semen analyses.

Plechaty et al. (1977) measured lead concentrations in the semen of 21 healthy men. Semen lead levels were generally less than blood lead levels, and no correlation was found between lead content of the semen and sperm counts or blood lead levels in this small sample.

Hypothalamic-pituitary-testicular relationships were investigated by Braunstein et al. (1978) in men occupationally exposed at a lead smelter. Six subjects had 2-11 years of exposure to lead and exhibited marked symptoms of lead toxicity. All had received one or more courses of EDTA chelation therapy. This group was referred to as "lead-poisoned" (LP). Four men from the same smelter had no signs of lead toxicity, but had been exposed for 1-23 years and were designated "lead-exposed" (LE). The control (C) group consisted of nine volunteers.

Mean (± standard error) blood lead levels for the LP, LE, and C groups were 38.7 (± 3), 29.0 (± 5), and 16.1 (± 1.7) µg/dl, respectively, at the time of the study. Previously, how-

ever, the LP and LE groups had exhibited values as high as 88.2 (± 4) and 80 (± 0) µg/dl, respectively. All three groups were chelated and 24-hour urinary lead excretion values were 999 (± 141), 332 (± 17), and 225 (± 31) µg for the LP, LE, and C groups, respectively. Frequency of intercourse was significantly less in both lead-exposed groups than in controls. Sperm concentrations in semen of the LP and LE men ranged from normal to severely oligospermic, and one from the LP group was unable to ejaculate. Testicular biopsies were performed on "the two most severely lead-poisoned men," one with aspermia and one with testicular pain. Both men showed increased peritubular fibrosis, decreased spermatogenesis, and Sertoli cell vacuolization. The two lead groups exhibited reduced basal serum testosterone levels, but displayed a normal increase in serum testosterone following stimulation with human chorionic gonadotrophin. A similar rise in serum follicle-stimulating hormone was seen following treatment with clomiphene citrate or gonadotrophin releasing hormone, although the LP men exhibited a lower than expected increase in luteinizing hormone (LH). The LE men also appeared to have a decreased LH response, but the difference was not significant.

The results of the Braunstein et al. (1978) study suggest that lead exposure at high levels may result in a defect in regulation of LH secretion at the hypothalamic-pituitary level, resulting in abnormal dynamics of LH secretion. They also indicate a likely direct effect on the testes, resulting in oligospermia and peritubular fibrosis. Nevertheless, the possibility remains that such effects may have been precipitated by the EDTA chelation therapy, and the numbers of men studied were quite small.

More recently, Wildt et al. (1983) compared two groups of men exposed to lead in a Swedish battery factory. The 29 high-lead group men had had blood lead levels $\geq$50 µg/dl at least once prior to the study, while the 30 "controls" seldom exceeded 30 µg/dl. There were two test periods eight months apart. For the first test, 15 men were in the high lead and 24 in the control groups, respectively, and 17 were in each group for the second test. Fourteen and 15 of these men from the high lead and control groups, respectively, took part in both tests. Blood lead values were obtained periodically over a six-month period. For the two high lead groups, blood lead values were 46.1 and 44.6 µg/dl, respectively (range 25-75); corresponding values for the controls were 31.1 and 21.5 µg/dl (range 8-39). The high lead men tended to exhibit decreased function of the prostate and/or seminal vesicles, as measured by seminal plasma constituents (fructose, acid phosphatase, Mg, and Zn); however, a significant difference was seen only in the case of zinc. More men in the high lead than in the control group had low semen volume values, but the numbers of individuals did not allow a reliable statistical analysis. The heads of sperm of high lead individuals were more likely to swell when exposed to a detergent solution, viz. sodium dodecyl sulfate (SDS), a test of functional maturity, but the values were still in a normal range. Conversely, the leakage of lactate dehydrogenase isoenzyme X (LDH-X) was greater in control semen samples.

The values for live and for motile sperm were lower in the control group. The data were skewed, however, by the presence of several of the same men with low values in the control groups for both sampling times. Another confounding factor was the fact that the high lead and control groups differed in a significant way: ten of the control men had present or past urogenital tract infections versus none in the high lead group, possibly explaining the incidence of control samples with lowered sperm motility and viability. The observed decrease in SDS resistance in sperm of high lead group men may have been related to their apparent abnormal prostatic function, or to an effect of lead on sperm maturation. In evaluating the above results, it must also be noted that even the "controls" had elevated blood lead levels.

12.6.1.3 Placental Transfer of Lead. The transfer of lead across the human placenta and its potential threat to the conceptus have been recognized for more than a century (Paul, 1860). Documentation of placental transfer of lead to the fetus and data on resulting fetal blood lead levels help to build the case for a potential, but as yet not clearly defined, threat of subtle embryotoxicity or other deleterious health effects.

The placental transfer of lead has been established, in part, by various studies that have disclosed measurable quantities of lead in human fetuses or newborns, as well as offspring of experimental animals. The relevant data on prenatal lead absorption have been reviewed in Chapter 10, Section 2.4 of this document, and thus work dealing only with lead levels will not be discussed further here.

12.6.1.4 Effects of Lead on the Developing Human.

12.6.1.4.1 Effects of lead exposure on fetal metabolism. Prenatal exposure of the conceptus to lead, even in the absence of overt teratogenicity, may be associated with other health effects. This is suggested by studies relating fetal and cord-blood levels to changes in fetal heme synthesis. Haas et al. (1972) examined 294 mother-infant pairs for blood lead and urinary ALA levels. The maternal blood lead mean was 16.89 µg/dl; and the fetal blood lead mean was 14.98 µg/dl, with a correlation coefficient of 0.54 ($p < 0.001$). In the infants, blood lead levels and urinary ALA were positively correlated ($r = 0.19$, $p < 0.01$), although the data were based on spot urines (which tends to limit their value). The full biological significance of the elevated ALA levels is not clear, but the positive correlation between lead in blood and urinary ALA for the group as a whole indicates that increased susceptibility of heme synthesis occurs at relatively low blood lead levels in the fetus or newborn infant.

Subsequently, Kuhnert et al. (1977) measured ALA-D activity and levels of erythrocyte lead in pregnant urban women and their newborn offspring. Cord erythrocyte lead levels ranged from 16 to 67 µg/100 ml of cells, with a mean of 32.9. Lead levels were correlated with inhibition of ALA-D activity ($r = -0.58$, $p < 0.01$), suggesting that typical urban lead exposures could affect fetal enzyme activity. Note, however, that ALA-D activity is related to blood cell age, being highest in the younger cells. Thus, results obtained with cord blood, with

its high percentage of immature cells, are not directly comparable to those obtained with adult blood. In a later study, Lauwerys et al. (1978) found no lead-related increase in erythrocyte porphyrin levels in 500 mothers or their offspring. They did, however, report negative correlations between ALA-D activity and blood lead levels in both mothers and their newborns. Maternal blood lead levels averaged 10.2 µg/dl (range 3.1-31 µg/dl). Corresponding values for the newborns were 8.4 µg/dl and 2.7-27.3. Such results indicate that ALA-D activity may be a more sensitive indicator of fetal lead toxicity than erythrocyte porphyrin or urinary ALA levels.

12.6.1.4.2 Other toxic effects of intrauterine lead exposure. Fahim et al. (1976), in a study on maternal and cord-blood lead levels, determined blood lead values in women having preterm delivery and premature membrane rupture. Such women residing in a so-called "lead belt" (mining and smelting area) had significantly higher blood lead levels than women from the same area delivering at full term. Fahim et al. (1976) also noted that among 249 pregnant women in a control group outside the lead belt area, the percentages of women having preterm deliveries and premature rupture were 3 and 0.4, respectively, whereas corresponding values for the lead area (n = 253) were 13.04 and 16.99, respectively. A confusing aspect of this study, however, is the similarity of blood lead levels in women from the nonlead and lead belt areas. In fact, no evidence was presented that women in the lead belt group had actually received a greater degree of lead exposure during pregnancy than did control individuals. Also, questions exist regarding analytical aspects of this study. Specifically, other workers (e.g., see summary table in Clark, 1977) have typically found blood lead levels in mothers and their newborn offspring to be much more similar than those of Fahim et al. (1976).

In another study, Clark (1977) detected no effects of prenatal lead exposure in newborns with regard to birth weight, hemoglobin, or hematocrit. He compared children born of 122 mothers living near a Zambian lead mine with 31 controls from another area. Maternal and infant blood lead levels for the mine area were 41.2 (± 14.4) and 37.9 (± 15.3) µg/dl, respectively. Corresponding values for control mothers and offspring were 14.7 (± 7.5) and 11.8 (± 5.6) µg/dl.

There is also some evidence that lead levels in bone samples from stillborn children are higher than would be expected (Khera et al., 1980; Bryce-Smith et al., 1977), but the data are inconclusive.

Nordström et al. (1979b) examined birth weight records for offspring of female employees of the Rönnskär smelter and found decreased birth weights related to: (1) employment of the mothers at the smelter during pregnancy, (2) distance that the mothers lived from the smelter, and (3) proximity of the mother's job to the actual smelting process. Similar results were also seen for children born to mothers merely living near the smelter (Nordström et al., 1978a). Nordström et al. (1979b) also investigated birth defects in offspring of the female

smelter workers and in populations living at various distances from the Rönnskär smelter. They concluded that the frequencies of both single and multiple malformations were increased when the mother worked at the smelter during pregnancy.

The number of smelter workers with malformed offspring was relatively small (39/1291). The incidence of children with birth defects whose mothers worked while pregnant was 5.8 percent (17 of 291). Five of the six offspring with multiple malformations were in this group, suggesting that the observed effect may have been a real one. Nevertheless, the crucial factor in evaluating all of the Rönnskär studies is the exposure of workers and the nearby population to a number of toxic substances including not only lead, but arsenic, mercury, cadmium, and sulfur dioxide as well.

Alexander and Delves (1981) found that the mean blood lead concentrations of pregnant and non-pregnant control women living in an urban area of England were approximately 4 μg/dl higher than those for similar groups living in a rural area. The mean concentrations for the urban and rural pregnant women were 15.9 and 11.9 μg/dl, respectively ($p < 0.001$), but there were no demonstrable effects of the higher maternal blood lead levels on any aspect of perinatal health. The rate for congenital abnormality was higher in the rural area, suggesting that whatever the cause, it was unlikely to be related to maternal levels of lead.

Additional studies of placental lead and stillbirths have not clarified the situation. Khera et al. (1980) measured placental and stillbirth tissue lead in occupationally exposed women in the United Kingdom. Regardless of the incidence of stillbirths, placental lead concentrations were found to increase with duration of occupational exposure, from 0.29 μg/g at <1 yr exposure to 0.48 μg/g at >6 yr exposure for a group of 26 women aged 20-29 years. Placental lead concentrations also increased with age of the mother, independently of time of occupational exposure, and ranged from 0.30 (± 0.16) μg/g for those <20 yrs old to 0.51 (± 0.44) μg/g for those ≥30 yrs old. Average placental lead concentrations for 20 occupationally exposed women whose babies were stillborn were higher [0.45 (± 0.32) μg/g] than the average level of 0.29 (± 0.09) μg/g for placentas from eight mothers who had not been occupationally exposed for at least two years. The authors noted, however, that it was not possible to say whether occupational exposure caused any of the stillbirths or whether the high lead levels were merely consequential to the fetal death. It is somewhat disconcerting that the placental lead concentrations were about three times lower than those reported earlier by this group (Wibberley et al., 1977). These differences were attributed to methodological changes and to changes in concentration during storage of placentas at -20°C (Khera et al., 1980).

The placental lead concentrations reported by Alexander (1982) are, however, similar to the earlier results of Wibberley et al. (1977), with mean values of 1.34 (± 0.15) μg/g for seven stillbirths and 1.27 (± 0.48) μg/g for seven matched healthy controls. The wide range of concentrations reported for the controls (0.34-5.56 μg/g) and the differences in concentra-

tion with site of sampling makes it difficult to draw any useful conclusions from the results presented by Alexander. Clearly these analytical discrepancies in placental lead measurements must be resolved if any interpretation of their significance is to be made.

An additional study by Roels et al. (1978b) reported placental lead values of 0.08 (± 0.05) µg/g (range = 0.01-0.40 µg/g) from a variety of locations in Belgium, but these data indicated no correlation between lead concentration and birth weight. In contrast, placental lead has been reported to be associated with decreased activity of a placental enzyme, steroid sulfatase (Karp and Robertson, 1977). A similar association was found for mercury, suggesting that either metal or both together could have affected the enzyme activity or that the authors had merely uncovered a spurious correlation.

12.6.1.4.3 Paternally mediated effects of lead. There is increasing evidence that exposure of male laboratory animals to toxic agents can result in adverse effects on their offspring, including decreased litter size, birth weight, and survival. Mutagenic effects are the most likely cause of such results, but other mechanisms have been proposed (Soyka and Joffe, 1980). In the following cases, exposure of human males to lead has been implicated as the cause of adverse effects on the conceptus.

According to Koinuma (1926) in a brief report, 24.7 percent of workmen exposed to lead in a storage battery plant had childless marriages, while the value for men not so exposed was 14.8 percent. Rates for miscarriages or stillbirths in wives of lead-exposed men and controls were 8.2 and 2.8 percent, respectively, while corresponding figures for neonatal deaths were 24.2 and 19.2 percent. These comparisons were based on 170 lead-exposed and 128 control men. These differences in fertility and prenatal mortality, while not dramatic, are suggestive of a male-mediated lead effect; however, the reliability of the methodology used in this study cannot be determined, due to the brevity of the report.

In a study of the pregnancies of 104 Japanese women before and after their husbands began lead-smelter work, miscarriages increased to 8.30 percent of pregnancies from a pre-exposure rate of 4.70 percent (Nogaki, 1957). The miscarriage rate for 75 women whose husbands were not occupationally exposed to lead was 5.80 percent. In addition, exposure to lead was related to a significant increase in the ratio of male to female offspring at birth. Lead content of paternal blood ranged from 11 to 51.7 µg/dl [mean = 25.4 (± 1.26) µg/dl], but was not correlated with reproductive outcome, except in the case of the male to female offspring ratio. The reported blood lead levels appear low, however, in view of the occupational exposure of these men, and were similar to those given for controls [mean = 22.8 (± 1.63) µg/dl]. Also, maternal age and parity appear not to have been well controlled for in the analysis of the reproductive data. Another report (Van Assen, 1958) on fatal birth defects in children conceived during a period when their fathers were lead poisoned (but neither before nor after) also hints at paternally-mediated effects of lead.

In the above study by Nordström et al. (1979b), women employed at the Rönnskär smelter were found to have higher abortion rates if their husbands were also employed at the smelter. This was true only of their third or later pregnancies, however, suggesting that the effect was related to long-term exposure of the male gametogenic stem cells. Whether this was a lead effect or that of other toxins from the smelter is not clear.

12.6.1.5 Summary of the Human Data. The literature on the effects of lead on human reproduction and development leaves little doubt that lead can, at high exposure levels, exert significant adverse health effects on reproductive functions. Most studies, however, only looked at the effects of prolonged moderate to high exposures to lead, e.g., those encountered in industrial situations, and many reports do not provide definite information on exposure levels or blood lead levels at which specific effects were observed. Also the human data were derived from studies involving relatively small numbers of individuals and therefore do not allow for discriminating statistical analysis. These reports are often additionally confounded by failure to obtain appropriate controls and, in some cases, by the presence of additional toxic agents or disease states. These and other factors obviously make interpretation of the data difficult. It appears possible that effects on sperm or on the testis may occur due to chronic exposure resulting in blood lead values of 40-50 µg/dl, based on the Lancranjan et al. (1975) and Wildt et al. (1983) studies, but additional data are greatly needed. Exposure data related to reproductive functions in the female are so lacking that even a rough estimate is impossible. Data on maternal exposure levels at which effects may be seen in human fetuses or infants are also quite meager, although the results of Haas et al. (1972), Kuhnert et al. (1977), and Lauwerys et al. (1978) suggest possible perinatal effects on heme metabolism at maternal blood levels considerably below 30 µg/dl. The human data on actual absorbed doses are even more lacking than those on blood lead values, adding to the imprecision of conclusions relating lead exposure to reproductive outcome.

12.6.2 Animal Studies

12.6.2.1 Effects of Lead on Reproduction.

12.6.2.1.1 Effects of lead on male reproductive functions. Among the first investigators to report infertility in male animals due to lead exposure were Puhac et al. (1963), who exposed rats to lead via their diet. Ability to sire offspring returned, however, 45 days after cessation of treatment. More recently, Varma et al. (1974) gave a solution of lead subacetate in drinking water to male Swiss mice for four weeks (mean total intake of lead = 1.65 g). The fertility of treated males was reduced by 50 percent. Varma and coworkers calculated the mutagenicity index (number of early fetal deaths/total implants) to be 10.4 for lead-treated mice versus 2.98 for controls ($p < 0.05$). The major differences in fecundity appeared to have been due to differing pregnancy rates, however, rather than prenatal mortality. Impairment of

male fertility by lead rather than lead-induced mutagenicity was thus likely to have been the primary toxic effect observed. Additionally, it has been suggested by Léonard et al. (1973), that effects seen following administration of lead acetate in water may be due to resulting acidity, rather than to lead. Also, Eyden et al. (1978) found no decrease in fertility of male mice fed 0.1 percent lead acetate in the diet for 64 weeks.

Several animal studies have found lead-associated damage to the testes or prostate, generally at relatively high doses. Golubovich et al. (1968) found a decrease in normal spermatogonia in the testes of rats gavaged for 20 days with lead (2 mg/kg/day). Desquamation of the germinal epithelium of the seminiferous tubules was also increased, as were degenerating spermatogonia. Hilderbrand et al. (1973) also noted testicular damage in male rats given oral lead (100 µg/day for 30 days). Egorova (cited in Stöfen, 1974) injected lead at a dose of 2 µg/kg six times over a ten-day period and reported testicular damage.

Ivanova-Chemishanska et al. (1980) investigated the effect of lead on male rats administered 0.0001 or 0.01 percent solutions of lead acetate over a four-month period. The authors reported that changes in enzymatic activity and in levels of disulfide and ATP were observed in testicular homogenates. No histopathological changes in testicular tissue were found, but the fertility index for treated males was decreased. Offspring of those males exhibited postpartum "failure to thrive" and stunted growth. Such data suggest biological effects due to chronic lead exposure of the male, but the study is difficult to evaluate due to limited information on the experimental methods, particularly the dose levels actually received.

In a more recent study of lead effects on the male reproductive tract, no histopathological changes were seen during an examination of the testes of rabbits (Willems et al., 1982). Five males per group were dosed subcutaneously with up to 0.5 mg/kg lead acetate three times weekly for 14 weeks. Blood lead levels at termination of treatment were 6.6 and 61.5 µg/dl for control and high dose rabbits, respectively.

Lead-related effects on spermatozoa have also been published. For example, Stowe et al. (1973) reported the results of a low calcium and phosphate diet containing 100 ppm lead (as acetate) fed to dogs from 6 to 18 weeks of age. This dose resulted in a number of signs of toxicity, including spermatogonia with hydropic degeneration. In the Maisin et al. (1975) study, male mice received up to 1 percent lead in the diet, and the percentage of abnormal spermatozoa increased with increasing lead exposure. Eyden et al. (1978) also fed 1 percent lead acetate in the diet to male mice. By the eighth week, abnormal sperm had increased; however, the affected mice showed weight loss and other signs of general toxicity. Thus, the spermatogenesis effect was not indicative of differential sensitivity of the gonad to lead.

Krasovskii et al. (1979) observed decreased motility, duration of motility, and osmotic stability of sperm from rats given 0.05 mg/kg lead orally for 20-30 days. Damage to gonadal

blood vessels and to Leydig cells was also seen. Rats treated for 6-12 months exhibited abnormal sperm morphology and decreased spermatogenesis. In the report of Willems et al. (1982) described above, however, no effects on sperm count or morphology were seen in rabbits.

Lead acetate effects on sperm morphology were also tested in mice given about one sixteenth to one half an LD_{50} dose by i.p. injection on five consecutive days (Bruce and Heddle, 1979; Wyrobek and Bruce, 1978; Heddle and Bruce, 1977). The two lowest doses (apparently 100 and 250 mg/kg) resulted in only a modest increase in morphologically abnormal sperm 35 days after treatment, but the 500 or 900 mg/kg doses resulted in up to 21 percent abnormal sperm.

That lead could directly affect developing sperm or their cellular precursors is made more plausible by the data of Timm and Schulz (1966), who found lead in the seminiferous tubules of rats and in their sperm. The mechanisms for lead effects on the male gonad or gamete are unknown, however, although Golubovich et al. (1968) found altered RNA levels in the testes of lead exposed rats. They suggested that testicular damage was related to diminished ribosomal activity and inhibition of protein synthesis. As noted above, Ivanova-Chemishanska et al. (1980) observed biochemical changes in testes of lead-treated mice. Nevertheless, such observations are only initial attempts to determine a mechanism for observed lead effects. A more likely mechanism for such effects on the testis may be found in the work of Donovan et al. (1980), who found that lead inhibited androgen binding by the cytosolic receptors of mouse prostate. This could provide a mechanism for the observation of Khare et al. (1978), who found that injection of lead acetate into the rat prostate resulted in decreased prostatic weight; no such changes were seen in other accessory sex glands or in the testes.

Effects on hormonal production or on hormone receptors could also explain the results of Maker et al. (1975), who observed a delay in testicular development and an increase in age of first mating in male mice of two strains whose dams were given 0.08 percent lead (C57B1/6J) or 0.5 percent lead (Swiss-Webster albino) during pregnancy and lactation. The weanling males were fed these same doses in their diets through 60 days of age.

Another potential mechanism underlying lead effects on sperm involves its affinity for sulfhydryl groups. Mammalian sperm possess high concentrations of sulfhydryls believed to be involved in the maintenance of motility and maturation via regulation of stability in sperm heads and tails (Bedford and Calvin, 1974; Calvin and Bedford, 1971). It has also been found that blockage of membrane thiols inhibits sperm maturation (Reyes et al., 1976).

12.6.2.1.2 Effects associated with exposure of females to lead. Numerous studies have focused on lead exposure effects in females. For example, effects of lead on reproductive functions of female rats were studied by Hilderbrand et al. (1973), using animals given lead acetate orally at doses of 5 and 100 µg for 30 days. Control rats of both sexes had the same blood lead levels. Blood lead levels of treated females were higher than those of similarly treated males: 30 versus 19 µg/dl at the low dose, and 53 versus 30 µg/dl at the high dose.

The females exhibited irregular estrus cycles at both doses. When blood lead levels reached 50 µg/dl, they developed ovarian follicular cysts, with reductions in numbers of corpora lutea.

In a subsequent study (Der et al., 1974), lead acetate (100 µg lead per day) was injected s.c. for 40 days in weanling female rats. Treated rats received a low-protein (4 percent) or adequate-protein (20 percent) diet; controls were given the same diets without lead. Females on the low protein, high lead diet did not display vaginal opening during the treatment period and their ovaries decreased in weight. No estrous cycles were observed in animals from either low protein group; those of the adequate diet controls were normal, while those of the rats given adequate protein plus lead were irregular in length. Endometrial proliferation was also inhibited by lead treatment. Blood lead levels were 23 µg/dl in the two control groups, while values for the adequate and low protein lead-treated groups were 61 and 1086 µg/dl, respectively. The reports of Hilderbrand et al. (1973) and Der et al. (1974) suggest that lead chronically administered in high doses can interfere with sexual development in rats and the body burden of lead is greatly increased by protein deprivation.

Maker et al. (1975) noted a delay in age at first conception in female mice of two strains exposed to 0.08 percent (C57B1/6J) or 0.5 percent lead (Swiss-Webster) indirectly via the maternal diet (while in utero and nursing) and directly up to 60 days of age. These females were retarded in growth and tended to conceive only after reaching weights approximating those at which untreated mice normally first conceive. Litters from females that had themselves been developmentally exposed to at least 0.5 percent lead had lower survival rates and retarded development. More recently, Grant et al. (1980) reported delayed vaginal opening in rats whose mothers were given 25, 50, or 250 ppm lead (as lead acetate) in their drinking water during gestation and lactation followed by equivalent exposure of the offspring after weaning. The vaginal opening delays in the 25 ppm females occurred in the absence of any growth retardation or other developmental delays, in association with median blood lead levels of 18-29 µg/dl.

Although most animal studies have used rodents, Vermande-Van Eck and Meigs (1960) administered lead chloride i.v. to female rhesus monkeys. The monkeys were given 10 mg/ week for four weeks and 20 mg/week for the next seven months. Lead treatment resulted in cessation of menstruation, loss of color of the "sex skin" (presumably due to decreased estrogen production), and pathological changes in the ovaries. One to five months after lead treatment ceased menstrual periods resumed, the sex skin returned to a normal color, and the ovaries regained their normal appearance. Thus, there was an apparent reversal of lead effects on female reproductive functions, although there were no confirmatory tests of fertility.

The above studies indicate that pre- and/or post-natal exposure of female animals to lead can affect pubertal progression and hypothalamic-pituitary-ovarian-uterine functions. The

observations of delayed vaginal opening may reflect delayed ovarian estrogen secretion, suggesting toxicity to the ovary, hypothalamus, or pituitary. One study has demonstrated decreased levels of circulating follicle-stimulating hormone (Petrusz et al., 1979), and others discussed previously have shown lead-induced ovarian atrophy (Stowe and Goyer, 1971; Vermande-Van Eck and Meigs, 1960), again suggesting toxicity involving the hypothalamic-pituitary-ovarian-endometrial axis.

12.6.2.2 Effects of Lead on the Offspring. This section discusses developmental studies of offspring whose parents (one or both) were exposed to lead. Possible male-mediated effects as well as effects of exposure during gestation are reviewed. Results obtained for offspring of females given lead following implantation or throughout pregnancy are summarized in Tables 12-13 and 12-14.

12.6.2.2.1 Male mediated effects. A few studies have focused on male-mediated lead effects on the offspring, suggesting that paternally transmitted effects of lead may cause reductions in litter size, offspring weight, and survival rate.

Cole and Bachhuber (1914), using rabbits, were the first to report paternal effects of lead intoxication. In their study, the litters of dams sired by lead-intoxicated male rabbits were smaller than those sired by controls. Weller (1915) similarly demonstrated reduced birth weights and survival among offspring of lead-exposed male guinea pigs.

Offspring of lead-treated males from the Ivanova-Chemishanska et al. (1980) study described above were affected in a variety of ways, e.g. they exhibited "failure to thrive" and lower weights than did control progeny at one and three weeks postpartum. These results are difficult to interpret, however, without more specific information on the experimental methods and dosing procedures.

12.6.2.2.2 Results of lead exposure of both parents. Only a few studies have assessed the effects of lead exposure of both parents on reproduction. Schroeder and Mitchener (1971) found a reduction in the number of offspring of rats and mice given drinking water containing 25 ppm lead. According to the data of Schroeder et al. (1970), however, animals in the 1971 study may have been chromium deficient, and the Schroeder and Mitchener (1971) results are in marked contrast to those of an earlier study by Morris et al. (1938), who reported no significant reduction in weaning percentage among offspring of rats fed 512 ppm lead.

In another study, Stowe and Goyer (1971) assessed the relative paternal and maternal effects of lead as measured by effects on the progeny of lead-intoxicated rats. Female rats fed diets with or without 1 percent lead were mated with normal males. The pregnant rats were continued on their respective rations with or without lead throughout gestation and lactation. Offspring of these matings, the F_1 generation, were fed the rations of their dams and were mated in combinations as follows: control female to control male (CF-CM), control female to

TABLE 12-13. EFFECTS OF PRENATAL EXPOSURE TO LEAD ON THE OFFSPRING OF LABORATORY AND DOMESTIC ANIMALS: STUDIES USING ORAL OR INHALATION ROUTES OF EXPOSURE

Species	Test agent	Treatment		Effect on the offspring[a]			Reference
		Dose[b] and mode	Timing[c]	Mortality	Fetotoxicity	Malformation	
Rat	Lead acetate	512 ppm in diet	all	-	-	?	Morris et al. (1938)
		10,000 ppm in diet	all	+	+	?	Stowe and Goyer (1971)
	Lead acetate	45.2 mg/kg/day, po	6-16	-	-	-	Kennedy et al. (1975)
		45.5 mg/kg/day, po	6-8	+	+	-	
		31.9-47.8 mg/kg/day, po	all	-	-	-	Miller et al. (1982)
		63.7 mg/kg/day, po	all	-	+	-	
		150 mg/kg/day, po	6-18	+	-	-	Wardell et al. (1982)
		255-478 mg/kg/day in water	all,LAC	?	+[d]	?	Murray et al. (1978)
		31.9-319 ppm in water	all	±[e]	+	-	Dilts and Ahokas (1979, 1980)
		0.32-159 ppm in water	all	-	+	-	Kimmel et al. (1980)
	Tetraethyl lead	1.6-3.2 mg/kg/day, po	9-11 or 12-14	±	+	-	McClain and Becker (1972)
		0.064 mg/kg/day, po	6-16	-	-	-	Kennedy et al. (1975)
		0.64 mg/kg/day, po	6-16	+	+	-	
		6.4 mg/kg/day, po	6-8	+	+	-	
	Tetramethyl lead	10-28.7 mg/kg/day, po	9-11 or 12-14	±	+	-	McClain and Becker (1972)
	Trimethyl lead chloride	3.6-7.2 mg/kg/day, po	9-11 or 12-14	-	+	-	
	Lead nitrate	1 ppm in water	all	-	-	?	Hubermont et al. (1976)
		10 ppm in water	all	-	+[f,g]	?	
	Lead (aerosol)	1 or 3 mg/m^3, inhaled	1-21	?	-[f]	?	Prigge and Greve (1977)
		10 mg/m^3, inhaled	1-21	?	+[h]	?	
Mouse	Lead acetate	3,185 ppm in diet	1-7	+	±	N/A	Jacquet (1977)
		780-1,593 ppm in diet	1-16,17, or 18	?	+[f,i]	?	Jacquet et al. (1977b)
		3,185 ppm in diet	1-16,17, or 18	?	+[f,i,j]	?	
		1,593-6,370 ppm in diet	1-15,16, or 17	?	+[k]	?	Gerber and Maes (1978)
		1,595-3,185 ppm in diet	7-16,17, or 18	?	+[l]	?	Gerber et al. (1978)
		45.3 mg/kg/day, po	6-16	-	-	-	Kennedy et al. (1975)
		455 mg/kg/day, po	6-8	+	+	-	

TABLE 12-13. (continued)

Species	Test agent	Treatment: Dose[b] and mode	Treatment: Timing[c]	Effect on the offspring[a]: Mortality	Fetotoxicity	Malformation	Reference
Mouse		0.1-1.0 g/l in water	all	-	?	?	Léonard et al. (1973)
		637-3,185 ppm in diet	1-18	+	?	?	Maisin et al. (1975)
		1,593 ppm in diet	1-16,17, or 18	+	-	-	Jacquet et al. (1975)
		3,185 ppm in diet	1-16,17, or 18	+	+	-	
		1,250 ppm in diet	all	-	+	-	
		3,185 ppm in diet	1-16,17, or 18	+	+	-	
		1,250 ppm in diet	all	-	+	-	
		2,500-5,000 ppm in diet	all	+	+	-	Jacquet (1976)
		1,250 ppm in diet	all	-	+	-	
	Tetraethyl lead	0.06 mg/kg/day, po	6-16	-	-	-	Kennedy et al. (1975)
		0.64 mg/kg/day, po	6-16	+	+	-	
		6.4 mg/kg/day, po	6-8	+	+	-	
Sheep	Lead powder	0.5-16 mg/kg/day, in diet[l]	all	+	?	-	Sharma and Buck (1976)

[a] + = present; - = effect not seen; ± = ambiguous effect; ? = effect not examined or insufficient data.

[b] As elemental lead.

[c] Specific gestation days when exposed; LAC = also during lactation.

[d] Decreased numbers of dendritic spines and malformed spines at day 30 postpartum.

[e] Litter size values for high dose group suggestive of an effect.

[f] ALAD activity was decreased.

[g] Free tissue porphyrins increased in kidneys.

[h] Hematocrit was decreased.

[i] Fetal porphyrins were increased, except in the low dose fetuses assayed on gestation day 18.

[j] Decreased heme and fetal weight.

[k] Incorporation of Fe into heme decreased, and growth was retarded.

[l] Decreased placental blood flow.

TABLE 12-14. EFFECTS OF PRENATAL LEAD EXPOSURE ON OFFSPRING OF LABORATORY ANIMALS: RESULTS OF STUDIES EMPLOYING ADMINISTRATION OF LEAD BY INJECTION

Species	Test agent	Treatment		Effect on the offspring[a]			Reference
		Dose[b] and mode	Timing[c]	Mortality	Fetotoxicity	Malformation	
Rat	Lead acetate	15.9 mg/kg, ip	9	+	+	+	Zegarska et al. (1974)
	Lead nitrate	31.3 mg/kg, iv	8	-	+	+	McClain and Becker (1975)
		31.3 mg/kg, iv	9 or 16	+[d]	+	+	
		31.3 mg/kg, iv	10-14, 15,17		+	-	
		3.13 mg/kg, iv	9 or 15	-	-	-	Hackett et al. (1978a,b)
		15.6 mg/kg, iv	9	+	+	+	
		15.6 mg/kg, iv	15	+	?	?	
		unknown, iv	8 or 9	+	?	+	Coro Antich and Amoedo Mon (1980)
		31.3 mg/kg, iv	17	-	+	-	Minsker et al. (1982)
		15.6 mg/kg, iv	17	+	+	-	
		5 mg/kg, iv	9 or 15	-	-	-	Hackett et al. (1982)
		25 mg/kg, iv	9 or 15	+	+	+,-[e]	
	Lead chloride	7.5 mg/kg,[f]	9	±	-	-	McLellan et al. (1974)
		75 mg/kg,	9	+	+	-	
	Trimethyl lead chloride	20.2 mg/kg, iv	12	-	+	-	
		23.8 mg/kg, iv	9,10,13, or 15	+[g]	+	-	
Mouse	Lead acetate	9.56-22.3 mg/kg, ip	8	-	+	+	Jacquet and Gerber (1979)
		9.56 mg/kg, ip	9	+	-	+	
		22.3 mg/kg, ip	9	+	+	+	
		22.3 mg/kg, ip	10 or 12	-	-	-	
	Lead chloride	29.8 mg/kg, iv	3 or 4	+	?	?	Wide and Nilsson (1977)
		29.8 mg/kg, iv	6	+	N/A	N/A	

TABLE 12-14. (continued)

Species	Test agent	Treatment: Dose[b] and mode	Treatment: Timing[c]	Effect on the offspring[a]: Mortality	Fetotoxicity	Malformation	Reference
Hamster	Lead acetate	31.9 mg/kg, iv	8	+	?	+	Ferm (1969)
	Lead acetate or chloride	31.9 or 37.3 mg/kg, iv	8	?	?	+	Ferm and Carpenter (1967)
	Lead nitrate	31.3 mg/kg, iv	7, 8, or 9	?	?	+	Ferm and Carpenter (1967)
		15.6-31.3 mg/kg, iv	8 or 9	+	?	+	Ferm and Ferm (1971)
		31.3 mg/kg, iv	8	+	+	+	Carpenter and Ferm (1977)
		31.3 mg/kg, iv	8	+	+[h]	+	Gale (1978)

[a] + = effect present; - = effect not seen; ± = ambiguous effect; ? = effect not examined or insufficient data.

[b] As elemental lead.

[c] Specific gestation days when exposed.

[d] With the exception of day 17.

[e] No fetuses survived to be examined for malformation.

[f] No dosage route specified.

[g] Only after day 10 treatment.

[h] Delayed ossification (fetal weights not given).

[i] Dosage was varied daily to maintain a blood lead level of ≅ 40 µg/dl (range = 30 to 70 µg/dl).

lead-intoxicated male (CF-PbM), lead-intoxicated female to control male (PbF-CM), and lead-intoxicated female to lead-intoxicated male (PbF-PbM). The results are shown in Table 12-15.

The paternal effects of lead included reductions of 15 percent in the number of pups per litter, 12 percent in mean pup birth weight, and 18 percent in pup survival rate. The maternal effects of lead included reductions of 26 percent in litter size, 19 percent in pup birth weight, and 41 percent in pup survival. The combined male and female effects of lead toxicity resulted in reductions of 35 percent in the number of pups per litter, 29 percent in pup birth weight, and 67 percent in pup survival to weaning. Stowe and Goyer classified the effects of lead upon reproduction as gametotoxic, intrauterine, and extrauterine. The gametotoxic effects of lead seemed to be irreversible and had additive male and female components. Intrauterine effects were presumed to be due to lead uptake by the conceptus, plus gametotoxic effects. The extrauterine effects were due to the passage of lead from the dam to the nursing pups, adding to the gametotoxic and intrauterine effects.

Léonard et al. (1973), however, found no effect on the reproductive performance of groups of 20 pairs of mice given lead in their drinking water over a nine-month period. Lead doses ranged from 0.1 to 1.0 g/l. A total amount of 31 g/kg was ingested at the high dose, equivalent to ingestion of 2.2 kg lead by a 70 kg man over the same time period.

12.6.2.2.3 Lead effects on implantation and early development. Numerous studies have been performed to elucidate mechanisms by which lead causes prenatal death. They suggest two mechanisms of action for lead, one on implantation and the other (mainly at higher doses) on fetal development. The latter is discussed primarily in Section 12.6.2.2.4.5.

Maisin et al. (1975) exposed female mice to dietary lead for 18 days after mating; both the number of pregnancies and surviving embryos decreased. Similarly, exposure of female mice to lead via their diet (0.125-1.00 percent) from mating to 16-18 days afterward (Jacquet, 1976; Jacquet et al., 1975) resulted in decreased pregnancy incidence and number of corpora lutea; increased number of embryos dying after implantation at the highest dosages; decreased body weights of surviving fetuses; and treated dam fatalities at the high dose.

Jacquet and co-workers also described effects of maternal dietary lead exposure on preimplantation mouse embryos (Jacquet, 1976; Jacquet et al., 1976). They found lead in the diet to be associated with retardation of cleavage in embryos, failure of trophoblastic giant cells to differentiate, and absence of an uterine decidual reaction. Maisin et al. (1978) also found delayed cleavage in embryos of mice fed lead acetate prior to mating and up to 7 days afterwards.

Giavini et al. (1980) further confirmed the ability of lead to affect the preimplantation embryo in studies of rats transplacentally exposed to lead nitrate, and Wide and Nilsson (1977, 1979) reported that inorganic lead had similar effects on mice. Jacquet (1978) was able to force implantation in that species by use of high doses of progesterone, while Wide

TABLE 12-15. REPRODUCTIVE PERFORMANCE OF F_1 LEAD-INTOXICATED RATS

Parameter	Type of mating			
	CF-CM	CF-PbM	PbF-CM	PbF-PbM
Litters observed	22	24	36	16
Pups per litter	11.90 ± 0.40[a]	10.10 ± 0.50	8.78 ± 0.30[b]	7.75 ± 0.50[c]
Pup birth weight, g	6.74 ± 0.15	5.92 ± 0.13[c]	5.44 ± 0.13[c,d]	4.80 ± 0.19[c,d,e]
Weaned rats per litter	9.84 ± 0.50	7.04 ± 0.77[c]	5.41 ± 0.74[c,d]	2.72 ± 0.70[c,d,e]
Survival rate, %	89.80 ± 3.20	73.70 ± 7.90	52.60 ± 7.20	30.00 ± 8.20[c,d,f]
$\frac{\text{Litter birth weight}}{\text{Dam breeding weight}}$, %	28.04 ± 1.30	22.30 ± 0.90[c]	19.35 ± 1.00[c]	15.38 ± 1.10[c,d,f]
$\frac{\text{Litter birth weight}}{\text{Dam whelping weight}}$, %	19.09 ± 0.80	15.97 ± 0.58[c]	14.28 ± 0.66[c]	11.58 ± 0.78[c,d,f]
$\frac{\text{Gestational gain}}{\text{Pups per litter}}$, g	11.54 ± 0.60	11.20 ± 0.74	11.17 ± 0.54	12.34 ± 1.24
Nonfetal gestational gain per fetus, g	3.93 ± 0.38	4.83 ± 0.47	4.15 ± 0.42	3.96 ± 0.46

[a]Mean ± S.E.M.

[b]Significantly ($p < 0.05$) less than mean for CF-CM.

[c]Significantly ($p < 0.01$) less than mean for CF-CM.

[d]Significantly ($p < 0.01$) less than mean for CF-PbM.

[e]Significantly ($p < 0.01$) less than mean for PbF-CM.

[f]Significantly ($p < 0.05$) less than mean for PbF-CM.

Source: Stowe and Goyer (1971).

(1980) determined that administration of estradiol-17β and progesterone could reverse the effects of lead on implantation. Wide suggested that the lead-induced implantation blockage was mediated by a decrease in endometrial responsiveness to both sex steroids. Jacquet (1976) and Jacquet et al. (1977b) had attributed lead-induced prevention of implantation in the mouse to a lack of endogenous progesterone alone, stating that estrogen levels were unaffected. Later, however, Jacquet et al. (1977a) stated that estrogen levels also decreased, a finding not supported by Wide and Wide (1980). The latter authors did find a lead-induced increase in uterine estradiol receptors, but no change in binding affinities.

In order to examine lead effects early in gestation, Wide and Nilsson (1977) examined embryos from untreated mice and from mothers given 1 mg lead chloride on days 3, 4, or 6 of pregnancy. Embryonic mortality was greater in lead-treated litters; in the day-6 group some abnormal embryos were observed by day 8. In a later experiment, Wide (1978) removed blastocysts from lead-treated mice. She found that they attached and grew normally during three days of in vitro culture. Other blastocysts from untreated mothers were cultured in media containing lead, and a dose-dependent decrease in the number of normally developing embryos was seen.

A study employing domestic sheep was reported by Sharma and Buck (1976), who fed lead powder to pregnant ewes throughout gestation. Levels in the diet were varied from 0.5 to 16 mg/kg/day in an effort to keep blood lead levels near 40 µg/dl (actual levels ranged from 30 to 70 µg/dl). Such treatment resulted in a greatly decreased lambing percentage but no gross malformations. However, the number of subjects was small.

12.6.2.2.4 Teratogenicity and prenatal toxicity of lead in animals.

12.6.2.2.4.1 High dose effects on the conceptus. Teratogenic effects refer to physical defects (malformations) in the developing offspring. Prenatal toxicity (embryotoxicity, fetotoxicity) includes premature birth, prenatal death, stunting, histopathological effects, and transient biochemical or physiological changes. Behavioral teratogenicity, consisting of behavioral alterations or functional (e.g., motor, sensory) deficits resulting from in utero exposure, is dealt with in Section 12.4 of this chapter.

Teratogenicity of lead, at high exposure levels, has been demonstrated in rodents and birds, with some results suggesting a species-related specificity of certain gross teratogenic effects. Ferm and Carpenter (1967), as well as Ferm and Ferm (1971), reported increased embryonic resorption and malformation rates when various lead salts were administered i.v. to pregnant hamsters. Teratogenic effects were largely restricted to the tail region, including malformations of sacral and caudal vertebrae resulting in absent or stunted tails. Gale (1978) found the same effects plus hydrocephalus, among six strains of hamsters and noted differences in susceptibility, suggesting a genetic component in lead-induced teratogenicity.

Zegarska et al. (1974) performed a study with rats injected with lead acetate at midgestation. They reported embryonic mortality and malformations. McClain and Becker (1975) subsequently administered lead nitrate i.v. to rats on one of days 8-17 of gestation, producing malformations and embryo- and feto-toxicity. Hackett et al. (1978, 1982a,b) also gave lead i.v. to rats and found malformations and high incidences of prenatal mortality. Minsker et al. (1982) gave lead i.v. to dams on day 17 of gestation and observed decreased birth weights, as well as decreased weight and survival by postpartum day 7.

In another study, Miller et al. (1982) used oral doses of lead acetate up to 100 mg/kg given daily to rats before breeding and throughout pregnancy and found fetal stunting at the high dose, but no other effects. Maternal blood lead values ranged from 80 to 92 µg/dl prior to mating and from 53 to 92 µg/dl during pregnancy. Pretreatment and control blood lead levels averaged 6 to 10 µg/dl. Also, Wardell et al. (1982) gavaged rats daily with lead doses of up to 150 mg/kg from gestation day 6 through day 18 and observed decreased prenatal survival at the high dose, but no malformations.

Ferm (1969) reported that teratogenic effects of i.v. lead in hamsters are potentiated in the presence of cadmium, leading to severe caudal dysplasia. This finding was duplicated by Hilbelink (1980). In addition to caudal malformations, lead appears to influence the morphology of the developing brain. For example, Murray et al. (1978) described a significant decrease in number of dendritic spines and a variety of morphological abnormalities of such spines in parietal cortex of 30-day-old rat pups exposed to lead during gestation and nursing, during the postweaning period only, or during both periods. Morphometric analysis of rats transplacentally exposed to lead indicated that cellular organelles were altered as a function of dose and stage of development at exposure (Klein et al., 1978). These results indicate that morphologically apparent effects of lead on the brain could be produced by exposure during pregnancy alone, a question not addressed by Murray et al. (1978).

A variety of studies relating neurobehavioral effects to prenatal lead exposure have also been published. These studies are discussed in Section 12.4.3 of this chapter.

12.6.2.2.4.2 Low dose effects on the conceptus. There is a paucity of information regarding the teratogenicity and developmental toxicity of prolonged low-level lead exposure. Kimmel et al. (1980) exposed female rats chronically to lead acetate via drinking water (0.5, 5, 50, and 250 µg/g) from weaning through mating, gestation, and lactation. They observed a decrease in fetal body length of female offspring at the high dose, and the female offspring from the 50 and 250 µg/g groups weighed less at weaning and showed delays in physical development. Maternal toxicity was evident in the rats given 25 µg/g or higher doses, corresponding to blood lead levels of 20 µg/dl or higher. Reiter et al. (1975) observed delays in the development of the nervous system in offspring exposed to 50 µg/g lead throughout gestation

and lactation. Whether these delays in development resulted from a direct effect of lead on the nervous system of the pups or reflect secondary changes (resulting from malnutrition, hormonal imbalance, etc.) is not clear. Whatever the mechanisms involved, these studies suggest that low-level, chronic exposure to lead may induce postnatal developmental delays.

12.6.2.2.4.3 Prenatal effects of organolead compounds. In an initial study of the effects of organolead compounds in animals, McClain and Becker (1972) treated rats orally with 7.5-30 mg/kg tetraethyl lead, 40-160 mg/kg tetramethyl lead, or 15-38 mg/kg trimethyl lead chloride, given in three divided doses on gestation days 9-11 or 12-14. The last compound was also given i.v. at doses of 20 to 40 mg/kg on one of days 8-15 of pregnancy. The highest dose of each agent resulted in maternal death, while lower doses caused maternal toxicity. At all dose levels, fetuses from dams given multiple treatment weighed less than controls. Single treatments at the highest doses tended to have similar effects. In some cases delayed ossification was observed. In addition, direct intra-amniotic injection of trimethyl lead chloride at levels up to 100 µg per fetus caused increasing fetal mortality.

Kennedy et al. (1975) administered tetraethyl lead by gavage to mice and rats during the period of organogenesis at dose levels up to 10 mg/kg. Maternal toxicity, prenatal mortality, and developmental retardation were noted at the highest doses in both species, although maternal treatment was discontinued after only three days due to excessive toxicity. In a subsequent study involving alkyl lead, Odenbro and Kihlström (1977) treated female mice orally with triethyl lead at doses of up to 3.0 mg/kg/day on days 3 to 5 following mating. The highest treatment levels resulted in decreased pregnancy rates, while at 1.5 mg/kg, lower implantation rates were seen. In order to elucidate the mechanism of implantation failure in organolead-intoxicated mice, Odenbro et al. (1982) measured plasma sex steroid levels in mice five days after mating. Levels of both estradiol and progesterone, but not estrone, were decreased following intraperitoneal triethyl lead chloride on days three and four of gestation. Such results suggest a hormonal mechanism for blockage of implantation, a finding also suggested for inorganic lead (Wide, 1980; Jacquet et al., 1977a).

12.6.2.2.4.4 Effects of lead on fetal physiology and metabolism. Biochemical indicators of developmental toxicity have been the subject of a number of investigations, as possible indicators of subtle prenatal effects. Hubermont et al. (1976) exposed female rats to lead in drinking water before mating, during pregnancy, and after delivery. In the highest exposure group (10 ppm), maternal and offspring blood lead values were elevated and approached 68 and 42 µg/dl, respectively. Inhibition of ALA-D and elevation of free tissue porphyrins were also noted in the newborns. Maternal diets containing up to 0.5 percent lead were associated with increased fetal porphyrins and decreased ALA-D activity by Jacquet et al. (1977a). Fetuses in the high dose group had decreased weights, but no data were presented on maternal weight gain or food consumption (which could have influenced fetal weight).

In the only inhalation exposure study (Prigge and Greve, 1977), rats were exposed throughout gestation to an aerosol containing 1, 3, or 10 mg Pb/m^3 or to a combination of 3 mg Pb/m^3 and 500 ppm carbon monoxide CO. Both maternal and fetal ALA-D activities were strongly inhibited by lead exposure in a dose-related manner. In the presence of lead plus CO, however, fetal (but not maternal) ALA-D activity was higher than in the group given lead alone, possibly due to the increase in total ALA-D seen in the CO-plus-lead treated fetuses. Fetal body weight and hematocrit were decreased in the high-dose lead group, while maternal values were unchanged, thus suggesting that the fetuses were more sensitive to lead effects than were the mothers. Granahan and Huber (1978) also reported decreased hematocrit, as well as reduced hemoglobin levels, in fetal rats from lead intoxicated dams (1000 ppm in the diet throughout gestation).

Gerber and Maes (1978) fed pregnant mice diets containing up to one percent lead from day 7 to 18 of pregnancy and determined levels of heme synthesis. Incorporation of iron into fetal heme was inhibited, but glycine incorporation into heme and protein was unaffected. Gerber et al. (1978) also found that dietary lead given late in gestation resulted in diminished placental blood flow but did not decrease uptake of a non-metabolizable amino acid, alpha-amino isobutyrate. The authors could not decide whether lead-induced fetal growth retardation was due to placental insufficiency or to the previously described reduction in heme synthesis (Gerber and Maes, 1978). They did not mention the possibility that the treated mothers may have reduced their food consumption, resulting in a reduced nutrient supply to the fetus, regardless of fetal ability to absorb nutrients.

More recently, Wardell et al. (1982) exposed rat fetuses in utero to lead by gavaging their pregnant mothers with 150 mg/kg lead from gestation days 6 to 18. On day 19, fetal limb cartilage was tested for ability to synthesize protein, DNA, and proteoglycans, but no adverse effects were seen.

12.6.2.2.4.5 Possible mechanisms of lead-induced teratogenesis. The reasons for the localization of many of the gross teratogenic effects of lead are unknown at this time. Ferm and Ferm (1971) have suggested that the observed specificity could be explained by an interference with specific enzymatic events. Lead alters mitochondrial function and enhances or inhibits enzymes (Vallee and Ulmer, 1972); any or all such effects could interfere with normal development. Similarly, inhibition of ALA has been suggested as a mechanism of teratogenesis by Cole and Cole (1976).

In an attempt to study the mechanics of lead induction of sacral-tail region malformations, Carpenter and Ferm (1977) examined hamster embryos treated at mid-gestation during the critical stage for response to teratogens in this species. The initial effects were edema of the tail region of embryos 30 hours after maternal exposure, followed by blisters and hema-

tomas. These events disrupted normal caudal development, presumably by mechanical displacement. The end results seen in surviving fetuses were missing, stunted, or malformed tails and anomalies of the lower spinal cord and adjacent vertebrae.

12.6.2.2.4.6 Maternal factors in lead-induced teratogenesis and fetotoxicity. Nutritional factors may also have a bearing on the prenatal toxicity of lead. Jacquet and Gerber (1979) reported increased mortality and defects in fetuses of mice given i.p. injections of lead while consuming a calcium deficient diet during gestation. In several treatment groups, lead-treated calcium deficient mothers had low blood calcium levels, while controls on the same diet had normal values. It is not certain how meaningful these data are, however, as there was no clear dose-response relationship within diet groups. In fact, fetal weights were said to be significantly higher in two of the lead-treated groups (on the normal diet) than in the untreated controls. Another problem with the study was that litter numbers were small.

Another study on interactions of lead with other elements was done by Dilts and Ahokas (1979), who exposed rats to lead in their drinking water throughout gestation. Controls were pair-fed or fed ad libitum. Lead treatment was said to result in decreased fetal weight, and dietary zinc supplementation was claimed to be associated with a protective effect against fetal stunting. The data presented do not allow differentiation of effects due to maternal stress (e.g., decreased food consumption) from direct effects on the fetus. Litter numbers were small, and some of the data were confusing (e.g., a lead-treated and a pair-fed group with very similar litter sizes and total litter weights, but rather dissimilar average fetal weights; live litter weight divided by live litter size does not give the authors' values for average fetal weight). Also, no data were given on maternal or fetal lead or zinc levels. In a further report on apparently the same animals as above, Dilts and Ahokas (1980) found that lead inhibited cell division and decreased protein contents of the fetal placentas, eviscerated carcasses, and livers. Such lead-related effects were not influenced by maternal zinc supplementation.

12.6.2.3 Effects of Lead on Avian Species. The effects of lead on the reproduction and development of various avian species have been studied by a number of investigators, primarily out of interest in the effects of lead shot ingested by wildlife or out of interest in an avian embryo model for the experimental analysis of ontogenetic processes. The relevance of such studies to the health effects of lead on humans is not clear. Consequently, these studies are not discussed further here.

12.6.3 Summary

The most clear-cut data described in this section on reproduction and development are derived from studies employing high lead doses in laboratory animals. There is still a need for

more critical research to evaluate the possible subtle toxic effects of lead on the fetus, using biochemical, ultrastructural, or behavioral endpoints. An exhaustive evaluation of lead-associated changes in offspring will require consideration of possible additional effects due to paternal lead burden. Neonatal lead intake via consumption of milk from lead-exposed mothers may also be a factor at times. Also, it must be recognized that lead effects on reproduction may be exacerbated by other environmental factors (e.g., dietary influences, maternal hyperthermia, hypoxia, and co-exposure to other toxins).

There are currently no reliable data pointing to adverse effects in human offspring following paternal exposure to lead, and the early studies of high dose exposure in pregnant women indicate toxic--but not teratogenic--effects on the conceptus. Effects on reproductive performance in women are not well documented, but industrial exposure of men to lead at levels resulting in blood lead values of 40-50 μg/dl appear to have resulted in altered testicular function. Unfortunately, the human data regarding lead effects during development currently do not lend themselves to accurate estimation of no-effect levels.

The paucity of human exposure data forces an examination of the animal studies for indications of threshold levels for effects of lead on the conceptus. It must be noted that the animal data are almost entirely derived from rodents. Based on these rodent data, it seems likely that fetotoxic effects have occurred in animals at chronic exposures to 600-1000 ppm lead in the diet. Subtle effects appear to have been observed at 10 ppm in the drinking water, while effects of inhaled lead have been seen at levels of 10 mg/m^3. With acute exposure by gavage or by injection, the values are 10-16 mg/kg and 16-30 mg/kg, respectively. Since humans are most likely to be exposed to lead in their diet, air, or water, the data from other routes of exposure are of less value in estimating harmful exposures. Indeed, it seems likely that teratogenic effects occur only when the maternal dose is given by injection.

Although human and animal responses may be dissimilar, the animal evidence does document a variety of effects of lead exposure on reproduction and development. Measured or apparent changes in production of or response to reproductive hormones, toxic effects on the gonads, and toxic or teratogenic effects on the conceptus have all been reported. The animal data also suggest subtle effects on such parameters as metabolism and cell structure that should be monitored in human populations. Well-designed human epidemiological studies involving large numbers of subjects are still needed. Such data could clarify the relationship of exposure levels and durations to blood lead values associated with significant effects and are needed for estimation of no-effect levels.

12.7 GENOTOXIC AND CARCINOGENIC EFFECTS OF LEAD

12.7.1 Introduction

Potential carcinogenic, genotoxic (referring to alteration in structure or metabolism of DNA), and mutagenic roles of lead are considered here. Epidemiological studies of occupationally exposed populations are considered first. Such studies investigate possible associations of lead with induction of human neoplasia. Epidemiological studies are important because they assess the incidence of disease in humans under actual ambient exposure conditions. However, such studies have many limitations that make it difficult to assess the carcinogenic activity of any specific agent. These include general problems in accurately determining the amount and nature of exposure to a particular chemical agent; in the absence of adequate exposure data it is difficult to determine whether each individual in a population was equally exposed to the agent in question. It is also often difficult to assess other factors, such as exposure to carcinogens in the diet, and to control for confounding variables that may have contributed to the incidence of any neoplasms. These factors tend to obscure the effect of lead alone. Also, in an occupational setting a worker is often exposed to various chemical compounds, making it more difficult to assess epidemiologically the injurious effect resulting specifically from exposure to one, such as lead.

A second approach considered here examines the ability of specific lead compounds to induce tumors in experimental animals. The advantage of these studies over epidemiological investigations is that a specific lead compound, its mode of administration, and level of exposure can be well defined and controlled. Additionally, many experimental procedures can be performed on animals that for ethical reasons cannot be performed on humans, thereby allowing a better understanding of the course of chemically induced injury. For example, animals may be sacrificed and necropsies performed at any desired time during the study. Factors such as diet and exposure to other environmental conditions can be well controlled, and genetic variability can be minimized by use of well established and characterized animal lines. One problem with animal studies is the difficulty of extrapolating such data to humans; however, this drawback is perhaps more important in assessing the toxicity of organic chemicals than in assessing inorganic agents. The injury induced by many organic agents is highly dependent upon reactive intermediates formed *in vivo* by the action of enzymatic systems (e.g., microsomal enzymes) upon the parent compound. Both qualitative and quantitative differences between the metabolic capabilities of humans and experimental animals have been documented (Neal, 1980). With inorganic compounds of lead, however, the element of interest undergoes little alteration *in vivo* and, therefore, the ultimate toxic agent is less likely to differ between experimental animals and humans (Costa, 1980). The carcinogenic action of most

organic chemicals is dependent upon activation of a parent pro-carcinogen, whereas most metallic carcinogens undergo little alteration in vivo to produce their oncogenic effects (Costa, 1980).

A third approach discussed below is in vitro studies. Animal carcinogen bioassays are presently the preferred means for assessing carcinogenic activity but they are extremely expensive and time consuming. As a result, much effort has been directed toward developing suitable in vitro tests to complement in vivo animal studies in evaluating potential oncogenicity of chemicals. The cell transformation assay has as its endpoint neoplastic transformation of mammalian cells and is among the most suitable in vitro systems because it examines cellular events closely related to carcinogenesis (Heck and Costa, 1982a). A general problem with this assay system, which is less troublesome with reference to metal compounds, is that it employs fibroblastic cells in culture, which lack many in vivo metabolic systems. Since lead is not extensively metabolized in vivo, addition of liver microsomal extracts (which has been attempted in this and similar systems) is not necessary to generate ultimate carcinogen(s) from this metal (see above). However, if other indirect factors are involved with lead carcinogenesis in vivo, then these might be absent in such culture systems (e.g., specific lead-binding proteins that direct lead interactions in vivo with oncogenically relevant sites). There are also technical problems related to the culturing of primary cells and difficulties with the final microscopic evaluation of morphological transformations, which are prone to some subjectivity. However, if the assay is performed properly it can be very reliable and reproducible. Modifications of this assay system (i.e., exposure of pregnant hamsters to a test chemical followed by culturing and examination of embryonic cells for transplacentally induced transformation) are available for evaluation of in vivo metabolic influences, provided that the test agent is transported to the fetus. Additionally, cryopreservation of primary cultures isolated from the same litter of embryos can control for variation in cell populations exposed to test chemicals and give more reproducible responses in replicate experiments (Pienta, 1980). A potential advantage of the cell transformation assay system is the possibility that cultured human cells can be transformed in vitro. Despite numerous attempts, however, no reproducible human-cell transformation system has yet been sucessfully established which has been evaluated with a number of different chemicals of defined carcinogenic activity.

Numerous processes have been closely linked with oncogenic development, and specific assay systems that utilize events linked mechanistically with cancer as an endpoint have been developed to probe whether a chemical agent can affect any of these events. These systems include assays for mutations, chromosomal aberrations, development of micronuclei, enhancement of sister chromatid exchange, effects on DNA structure, and effects on DNA and RNA polymerase. These assay systems have been used to examine the genotoxicity of lead and facilitate the

assessment of possible lead carcinogenicity. Chromosomal aberration studies are useful because human lymphocytes cultured from individuals after exposure to lead allow evaluation of genotoxic activity that occurred under the influence of an in vivo metabolic system. Such studies are discussed below in relationship to genotoxic effects of lead. However, a neoplastic change does not necessarily result, and evaluations of some less conspicuous types of chromosomal aberrations are somewhat subjective since microscopy is exclusively utilized in the final analyses. The sensitivity of detection of chromosomal changes also tends to be less than other measurable DNA effects, e.g., the induction of DNA repair. However, it is reasonable to assume that if an agent produces chromosomal aberrations it may have potential carcinogenic activity. Many carcinogens are also mutagenic and this fact, combined with the low cost and ease with which bacterial mutation assays can be performed, has resulted in wide use of these systems in determining potential carcinogenicity of chemicals. Mutation assays can also be performed with eukaryotic cells and several studies are discussed below that examined the mutagenic role of lead in these systems. However, in bacterial systems such as the Ames test, metal compounds with known human carcinogenic activity are generally negative and, therefore, this system is not useful for determining the potential oncogenicity of lead. Similarly, even in eukaryotic systems, metals with known human cancer-causing activity do not produce consistent mutagenic responses. Reasons for this lack of mutagenic effect remain unclear, and it appears that mutagenicity studies of lead cannot be weighed heavily in assessing its genotoxicity.

Other test systems that probe for effects of chemical agents on DNA structure may be useful in assessing the genotoxic potential of lead. Sister chromatid exchange represents the normal movement of DNA in the genome and enhancement of this process by potentially carcinogenic agents is a sensitive indicator of genotoxicity (Sandberg, 1982). However, these studies usually involve tissue cultures; consequently, in vivo interactions related to such effects have not been addressed with this system. Numerous recently developed techniques can be used to assess DNA damage induced by chemical carcinogens. One of the most sensitive is alkaline elution (Kohn et al., 1981), which may be used to study DNA lesions produced in vivo or in cell culture. This technique can measure DNA strand breaks or crosslinks in DNA, as well as repair of these lesions, but lead compounds have not been studied with this technique. Assessment of the induction of DNA repair represents one of the most sensitive techniques for probing genotoxic effects. The reason for this is that the other procedures measure DNA lesions that have persisted either because they were not recognized by repair enzymes or because their number was sufficiently great to saturate DNA repair systems. Measurement of DNA repair activation is still possible even if the DNA lesion has been repaired, but effects of lead compounds on DNA repair have not been studied. There are a few isolated experiments within publications that examined the ability of lead compounds to induce DNA damage, but this

line of investigation requires further work. There are some well-conducted studies of the effect of lead along with other water soluble metals on isolated DNA and RNA polymerases, which suggest mutagenic mechanisms occurring in intact cells. The ability of lead to affect the transcription of DNA and RNA merits concern in regard to its potential oncogenic and mutagenic properties.

12.7.2 Carcinogenesis Studies with Lead and its Compounds

12.7.2.1 Human Epidemiological Studies. Epidemiological studies of industrial workers, where the potential for lead exposure is usually greater than for a "normal population," have been conducted to evaluate the role of lead in the induction of human neoplasia (Cooper, 1976, 1981; Cooper and Gaffey, 1975; Chruściel, 1975; Dingwall-Fordyce and Lane, 1963; Lane, 1964; McMichael and Johnson, 1982; Neal et al., 1941; Nelson et al., 1982). In general, these studies made no attempt to consider types of lead compounds to which workers were exposed or to determine probable routes of exposure. Some information on specific lead compounds encountered in the various occupational settings, along with probable exposure routes, would have made the studies more interpretable and useful. As noted in Chapter 3, with the exception of lead nitrate and lead acetate, many inorganic lead salts are relatively water insoluble. If exposure occurred by ingestion, the ability of water-insoluble lead salts (e.g., lead oxide and lead sulfide) to dissolve in the gastrointestinal tract may contribute to understanding of their ultimate systemic effects in comparison to their local actions in the gastrointestinal tract. Factors such as particle size are also important in the dissolution of any water insoluble compounds in the gastrointestinal system (Mahaffey, 1983). When considering other routes of exposure (e.g., inhalation), the water solubility of the lead compound in question, as well as the particle size, are extremely important, both in terms of systemic absorption and contained injury in the immediate locus of the retained particle (see Chapter 10). A hypothetical example is the inhalation of an aerosol of lead oxide versus a water soluble lead salt such as lead acetate. Lead oxide particles having a diameter of <5 μm would tend to deposit in the lung and remain in contact with cells there until they dissolved, while soluble lead salts would dissipate systemically at a much more rapid rate. Therefore, in the case of inhaled particulate compounds, localized exposure to lead might produce injury primarily in respiratory tissue, whereas with soluble salts systemic (i.e., CNS, kidney, and erythropoietic) effects might predominate.

The studies of Cooper and Gaffey (1975) and Cooper (1976, 1981) examined the incidence of cancer in a large population of industrial workers exposed to lead. Two groups of individuals were identified as the lead-exposed population under consideration: smelter workers from six lead production facilities and battery plant workers (Cooper and Gaffey, 1975). The authors reported (see Table 12-16) that total mortality from cancer was higher in lead smelter workers

than in a control population in two ways: (1) the difference between observed and expected values for the types of malignancies reported; and (2) the standardized mortality ratio, which indicates a greater than "normal" response if it is in excess of 100 percent. These studies report not only an excess of all forms of cancer in smelter workers but also a greater level of cancer in the respiratory and digestive systems in both battery plant and smelter workers. The incidence of urinary system cancer was also elevated in the smelter workers (but not in the battery plant workers), although the number of individuals who died from this neoplasm was very small. As the table indicates, death from neoplasm at other sites was also elevated compared with a normal population, but these results were not discussed in the report. Kang et al. (1980) examined the Cooper and Gaffey (1975) report and noted an error in the statistical equation used to assess the significance of excess cancer mortality. Table 12-17, from Kang et al., 1980, shows results based on a corrected form of the statistical equation used by Cooper and Gaffy; it also employed another statistical test claimed to be more appropriate. Statistical significance was observed in every category listed with the exception of battery plant workers, whose deaths from all forms of neoplasia were not different from a control population.

TABLE 12-16. EXPECTED AND OBSERVED DEATHS FOR MALIGNANT NEOPLASMS JAN. 1, 1947 - DEC. 31, 1979 FOR LEAD SMELTER AND BATTERY PLANT WORKERS

Causes of Death (ICD† Code)	Smelters			Battery plant		
	Obs	Exp	SMR*	Obs	Exp	SMR+
All malignant neoplasms (140-205)	69	54.95	133	186	180.34	111
Buccal cavity & pharynx (140-248)	0	1.89	--	6	6.02	107
Digestive organs peritoneum (150-159)	25	17.63	150	70	61.48	123
Respiratory system (160-164)	22	15.76	148	61	49.51	132
Genital organs (170-179)	4	4.15	101	8	18.57	46
Urinary organs (180-181)	5	2.95	179	5	10.33	52
Leukemia (204)	2	2.40	88	6	7.30	88
Lymphosarcoma lymphatic and hematopoietic (200-203, 205)	3	3.46	92	7	9.74	77
Other sites	8	6.71	126	23	17.39	142

†International Classification of Diseases.

*Correction of +5.55% applied for 18 missing death certificates.

+Correction of +7.52% applied for 71 missing death certificates.

Source: Cooper and Gaffey (1975).

TABLE 12-17. EXPECTED AND OBSERVED DEATHS RESULTING FROM SPECIFIED MALIGNANT NEOPLASMS FOR LEAD SMELTER AND BATTERY PLANT WORKERS AND LEVELS OF SIGNIFICANCE BY TYPE OF STATISTICAL ANALYSIS ACCORDING TO ONE-TAILED TESTS

Causes of death (ICD† code)	Number of deaths		SMR*	Probability		
	Observed	Expected		Poisson**	This analysis***	Cooper and Gaffey****
Lead smelter workers:						
All malignant neoplasms (140-205)	69	54.95	133	<0.02	<0.01	<0.02
Cancer of the digestive organs peritoneum (250-159)	25	17.63	150	<0.03	<0.02	<0.05
Cancer of the respiratory system (160-164)	22	15.76	148	<0.05	<0.03	>0.05
Battery plant workers:						
All malignant neoplasms (140-205)	186	180.34	111	>0.05	>0.05	>0.05
Cancer of the digestive organs, peritoneum (150-159)	70	61.48	123	<0.05	<0.04	>0.05
Cancer of the respiratory system (160-164)	61	49.51	132	<0.03	<0.02	<0.03

†International Classification of Diseases.

*SMR values were corrected by Cooper and Gaffey for missing death certificates under the assumption that distribution of causes of death was the same in missing certificates as in those that were obtained.

**Observed deaths were recalculated as follows: adjusted observed deaths = (given SMR/100) x expected deaths.

***Given $z = (SMR - 100)\sqrt{expected}/100$.

****Given $z = (SMR - 100)/\sqrt{100 \times SMR/expected}$.

Source: Kang et al. (1980).

Cooper and Gaffey (1975) did not discuss types of lead compounds that these workers may have been exposed to in smelting operations, but workers thus employed likely ingested or inhaled oxides and sulfides of lead. Since these and other lead compounds produced in the industrial setting are not readily soluble in water it could be that the cancers arising in respiratory or gastrointestinal systems were caused by exposure to water-insoluble lead compounds. Although the Cooper and Gaffey (1975) study had a large sample (7032), only 2275 of the workers (32.4 percent) were employed when plants monitored urinary lead. Urinary lead values were available for only 9.7 percent of the 1356 deceased employees on whom the cancer

mortality data were based. Only 23 (2 percent) of the 1356 decedents had blood lead levels measured. Cooper and Gaffey (1975) did report some average urinary and blood lead levels, where 10 or more urine or at least three blood samples were taken (viz., battery plant workers: urine lead = 129 µg/l, blood lead = 67 µg/dl; smelter workers: urine lead = 73 µg/l, blood lead = 79.7 µg/dl). Cooper (1976) noted that these workers were potentially exposed to other materials, including arsenic, cadmium, and sulfur dioxide, although no data on such exposures were reported. In these and other epidemiological studies in which selection of subjects for monitoring exposure to an agent such as lead is left to company discretion, it is possible that individual subjects are selected primarily on the basis of obvious signs of lead exposure, while other individuals who show no symptoms of lead poisoning would not be monitored (Cooper and Gaffey, 1975). It is also not clear from these studies when the lead levels were measured, although the timing of measurement would make little difference since no attempt was made to match an individual's lead exposure to any disease process.

In a follow-up study of the same population of workers, Cooper (1981) concluded that lead had no significant role in the induction of neoplasia. However, he did report standardized mortality ratios (SMRs) of 149 percent and 125 percent for all types of malignant neoplasms in lead battery plant workers with < 10 and > 10 years of employment, respectively. SMR is a percentage value that is based upon comparison of an exposed population relative to a control population. If the value exceeds 100 percent, the incidence of death is greater than normal but not necessarily statistically significant. In battery workers employed for 10 years or more there was an unusually high incidence of cancer listed as "other site" tumors (SMR = 229 percent; expected = 4.85, observed = 16). Respiratory cancers were elevated in the battery plant workers employed for less than 10 years (SMR = 172 percent). Similarly, in workers involved with lead production facilities for more than 10 years the SMR was 151 percent. Again, in the absence of good lead exposure documentation, it is difficult to assess the contribution of lead to the observed results. Cooper (1981) suggested that the excess of respiratory cancers could have been due to a lack of correction for smoking histories.

A recent study (McMichael and Johnson, 1982) examined the historical incidence of cancers in a population of smelter workers diagnosed as having lead poisoning. The incidence of cancer in a relatively small group of 241 workers was compared with 695 deceased employees from the same company. The control group had been employed during approximately the same period and was asserted to be free from lead exposure, although there were no data to indicate lead levels in either the control or the experimental group. Based upon diagnoses of lead poisoning made in the 1920s and 1930s for a majority of the deaths, the authors concluded that there was a considerably lower incidence of cancer in lead-poisoned workers. However, there is no indication of how lead poisoning was diagnosed. It is difficult to draw any conclusions from this study with regard to the role of lead in human neoplasia.

Evaluation of the ability of lead to induce human neoplasia must await further epidemiological studies in which other factors that may contribute to the observed effects are well controlled for and the disease process is assessed in individuals with well documented exposure histories. Little can now be reliably concluded from available epidemiological studies.

12.7.2.2 Induction of Tumors in Experimental Animals. As discussed in the preceding sections it is difficult to obtain conclusive evidence of the carcinogenic potential of an agent using only epidemiological studies. Experiments testing the ability of lead to cause cancer in experimental animals are an essential aspect of understanding its oncogenicity in humans. However, a proper lifetime animal feeding study to assess the carcinogenic potential of lead following National Cancer Institute guidelines (Sontag et al., 1976) has not been conducted. The cost of such studies exceed $1 million and consequently are limited only to those agents in which sufficient evidence based upon in vitro or epidemiological studies warrants such an undertaking. The literature on lead carcinogenesis contains many smaller studies where only one or two doses were employed and where toxicological monitoring of experimental animals exposed to lead was generally absent. Some of these studies are summarized in Table 12-18. Most mainly serve to illustrate that numerous different laboratories have induced renal tumors in rats by feeding them diets containing 0.1 percent or 1.0 percent lead acetate. In some cases, other lead formulations were tested, but the dosage selection was not based upon lethal dose values. In most cases, only one dose level was used. Another problem with many of these studies was that the actual concentrations of lead administered and internal body burdens achieved were not measured. Some of these studies are discussed very briefly; others are omitted entirely because they contribute little to our understanding of lead carcinogenesis.

Administration of 1.0 percent lead acetate (10,000 ppm) resulted in kidney damage and a high incidence of mortality in most of the studies in Table 12-18. However, kidney tumors were also evident at lower dosages (e.g., 0.1 percent lead acetate in the diet), which produced less mortality among the test animals. As discussed in Section 12.5, renal damage is one of the primary toxic effects of lead. At 0.1 percent lead acetate (1000 ppm) in the diet, the concentration of lead measured in the kidney was 30 µg/g while 1 percent lead acetate resulted in 300 µg/g of lead in the kidneys of necropsied animals (Azar et al., 1973). In most of the studies with rats fed 0.1 or 1.0 percent lead in the diet, the incidence of kidney tumors increased between the lower and higher dosage, suggesting a relationship between the deposition of lead in the kidney and the carcinogenic response. Renal tumors were also induced in mice at the 0.1 percent oral dosage of lead subacetate but not in hamsters that were similarly exposed to this agent (Table 12-18).

Other lead compounds have also been tested in experimental animals, but in these studies only one or two dosages (generally quite high) were employed, making it difficult to assess

TABLE 12-18. EXAMPLES OF STUDIES ON THE INCIDENCE OF TUMORS IN EXPERIMENTAL ANIMALS EXPOSED TO LEAD COMPOUNDS

Species	Pb compound	Dose and mode	Incidence (and type) of neoplasms	Reference
Rat	Pb phosphate	120-680 mg (total dose s.c.)	19/29 (renal tumors)	Zollinger (1953)
Rat	Pb acetate	1% (in diet)	15/16 (kidney tumors) 14/16 (renal carcinomas)	Boyland et al. (1962)
Rat	Pb subacetate	0.1% and 1.0% (in diet)	11/32 (renal tumors) 13/24 (renal tumors)	Van Esch et al. (1962)
Mouse	Pb naphthenate	20% in benzene (dermal 1-2 times weekly)	5/59 (renal neoplasms) (no control with benzene)	Baldwin et al. (1964)
Rat	Pb phosphate	1.3 g (total dosage s.c.)	29/80 (renal tumors)	Balo et al. (1965)
Rat	Pb subacetate	0.5 - 1% (in diet)	14/24 (renal tumors)	Hass et al. (1967)
Rat	Pb subacetate	1% (in diet)	31/40 (renal tumors)	Mao and Molnar (1967)
Mouse	Tetraethyl lead in tricaprylin	0.6 mg (s.c.) 4 doses between birth and 21 days	5/41 (lymphomas) in females, 1/26 in males, and 1/39 in controls	Epstein and Mantel (1968)
Rat	Pb acetate	3 mg/day for 2 months; 4 mg/day for 16 months (p.o.)	72/126 (renal tumors) 23/94 males (testicular [Leydig cell] tumors)	Zawirska and Medraś (1968)
Hamster	Pb subacetate	1.0% (in 0.5% diet)	No significant incidence of renal neoplasms	Van Esch and Kroes (1969)
Mouse	Pb subacetate	0.1% and 1.0% (in diet)	7/25 (renal carcinomas) at 0.1% Substantial death at 1.0%	Van Esch and Kroes (1969)
Rat	Pb nitrate	25 g/l in drinking water	No significant incidence of tumors	Schroeder et al. (1970)
Rat	Pb acetate	3 mg/day (p.o.)	89/94 (renal, pituitary, cerebral gliomas, adrenal, thyroid, prostatic, mammary tumors)	Zawirska and Medraś, 1972

TABLE 12-18. (continued)

Species	Pb Compound	Dose and mode	Incidence (and type) of neoplasms	Reference
Rat	Pb acetate	0, 10, 50, 100, 1000, 2000 ppm (in diet) for 2 yr	No tumors 0-100 ppm; 5/50 (renal tumors) at 500 ppm; 10/20 at 1000 ppm; 16/20 males, 7/20 females at 2000 ppm	Azar et al. (1973)
Hamster	Pb oxide	10 intratracheal administrations (1 mg)	0/30 without benzopyrene, 12/30 with benzopyrene (lung cancers)	Kobayashi and Okamoto (1974)
Rat	Pb powder	10 mg orally 2 times each month	5/47 (1 lymphoma, 4 leukemias)	Furst et al. (1976)
		10 mg/monthly for 9 months; then 3 monthly injections of 5 mg	1/50 (fibrosarcoma)	

the potential carcinogenic activity of lead compounds at relatively nontoxic concentrations. It is also difficult to assess the true toxicity caused by these agents, since properly designed toxicity studies were generally not performed in parallel with these cancer studies.

As shown in Table 12-18, lead nitrate produced no tumors in rats when given at very low concentrations, but lead phosphate administered subcutaneously at relatively high levels induced a high incidence of renal tumors in two studies. Lead powder administered orally resulted in lymphomas and leukemia; when given intramuscularly only one fibrosarcoma was produced in 50 animals. Lead naphthenate applied as a 20 percent solution in benzene two times each week for 12 months resulted in the development of four adenomas and one renal carcinoma in a group of 50 mice (Baldwin et al., 1964). However, in this study control mice were not painted with benzene. Tetraethyl lead at 0.6 mg given in four divided doses between birth and 21 days to female mice resulted in 5/36 surviving animals developing lymphomas while 1/26 males treated similarly and 1/39 controls developed lymphomas (Epstein and Mantel, 1968).

Lead subacetate has also been tested in the mouse lung adenoma bioassay (Stoner et al., 1976). This assay measures the incidence of nodules forming in the lung of strain A/Strong mice following parenteral administration of various test agents. Nodule formation in the lung does not actually represent the induction of lung cancer but merely serves as a general measure of carcinogenic potency independent of lung tissue (Stoner et al., 1976). Lead subacetate was administered to mice at 150, 75, and 30 mg (total dose), which represented the maximum

tolerated dose (MTD), 1/2 MTD, and 1/5 MTD, respectively, over a 30-week period using 15 separate i.p. injections (Stoner et al., 1976). Survivals at the three doses were 15/20 (MTD), 12/20 (1/2 MTD), and 17/20 (1/5 MTD), respectively, with 11/15, 5/12, and 6/17 survivors having lung nodules. Only at the highest doses was the incidence of nodules greater than in the untreated 1 or 2 highest groups. However, these authors concluded that on a molar-dose basis lead subacetate was the most potent of all the metallic compounds examined. Injection of 0.13 mmol/kg lead subacetate was required to produce one lung tumor per mouse, indicating that this compound was about three times more potent than urethane (at 0.5 mmol/kg) and approximately 10 times more potent than nickelous acetate (at 1.15 mmol/kg). The mouse lung adenoma bioassay has been one of the most utilized systems for examining carcinogenic activity in experimental animals and is well recognized as a highly accurate test system for assessing potential carcinogenic hazard (Stoner et al., 1976). Lead oxide combined with benzopyrene administered intratracheally resulted in 11 adenomas and 1 adenocarcinoma in a group of 15 hamsters, while no lung neoplasias were observed in groups receiving benzopyrene or lead oxide alone (Kobayashi and Okamoto, 1974).

Administration of lead acetate to rats has been reported to produce other types of tumors, e.g., testicular, adrenal, thyroid, pituitary, prostate, lung (Zawirska and Medras, 1968), and cerebral gliomas (Oyasu et al., 1970). However, in other animal species, such as dogs (Azar et al., 1973; Fouts and Page, 1942) and hamsters (Van Esch and Kroes, 1969), lead acetate induced either no tumors or only kidney tumors (Table 12-18).

The above studies seem to implicate some lead compounds as carcinogens in experimental animals but were not designed to address the question of lead carcinogenesis in a definitive manner. In contrast, a study by Azar et al. (1973) examined the oncogenic potential of lead acetate at a number of doses and in addition monitored a number of toxicological parameters in the experimental animals. Azar et al. (1973) gave 0, 10, 50, 100, 1000 and 2000 ppm dose levels of lead (as lead acetate) to rats during a two-year feeding study. Fifty rats of each sex were utilized at doses of 10 to 500 ppm, while 100 animals of each sex were used as controls. After the study was under way for a few months, a second 2-year feeding study was initiated using 20 animals of each sex in groups given doses of 0, 1000, or 2000 ppm. The study also included four male and four female beagle dogs at each dosage of lead ranging from 0 to 500 ppm in a 2-year feeding study. During this study, the clinical appearance and behavior of the animals were observed, and food consumption, growth, and mortality were recorded. Blood, urine, fecal, and tissue lead analyses were done periodically using atomic absorption spectrophotometry. A complete blood analysis was done periodically, including blood count, hemoglobin, hematocrit, stippled cell count, prothrombin time, alkaline phosphatase, urea nitrogen, glutamic-pyruvate transaminase, and albumin-to-globulin ratio. The activity of the enzyme alpha-aminolevulinic acid dehydrase (ALA-D) in the blood and the excretion of its sub-

strate, delta-aminolevulinic acid (δ-ALA) in the urine were also determined. A thorough necropsy, including both gross and histologic examination, was performed on all animals. Reproduction was also assessed (see Section 12.6).

Table 12-19 depicts the mortality and incidence of kidney tumors reported by Azar et al. (1973). At 500 ppm (0.05 percent) and above, male rats developed a significant number of renal tumors. Female rats did not develop tumors except when fed 2000 ppm lead acetate. Two out of four male dogs fed 500 ppm developed a slight degree of cytomegaly in the proximal convoluted tubule but did not develop any kidney tumors. The number of stippled red blood cells increased at 10 ppm in the rats but not until 500 ppm in the dogs. ALA-D was decreased at 50 ppm in the rats but not until 100 ppm in the dogs. Hemoglobin and hematocrit, however, were not depressed in the rats until they received a dose of 1000 ppm lead. These results illustrate that the induction of kidney tumors coincides with moderate to severe toxicological doses of lead acetate, for it was at 500-1000 ppm lead in the diet that a significant increase in mortality occurred (see Table 12-19). At 1000 and 2000 ppm lead, 21-day-old weanling rats showed no tumors but did show histological changes in the kidney comparable to those seen in adults receiving 500 ppm or more lead in their diet. Also of interest from the Azar et al. (1973) study is the direct correlation obtained in dogs between blood lead level and kidney lead concentrations. A dietary lead level of 500 ppm produced a blood lead concentration of 80 µg/dl, which corresponds to a level at which humans often show clinical signs of lead poisoning (see Section 12.4.1). The kidney lead concentration corresponding to this blood lead level was 2.5 µg/g (wet weight), while at 50 µg/dl in blood the kidney lead levels were 1.5 µg/g. Presumably blood and kidney lead were determined at about the same time, although this was not clear from the report. At this level of lead, kidney tumors were induced in the rats but not the dogs. However, it is apparent from the above differences in hematological parameters that dogs tolerate higher levels of lead than rats. As shown in Figure 12-5, the induction of renal tumors by lead acetate was linearly proportional to the dietary levels of lead fed to male rats. It may be concluded, therefore, that chronic lead exposure of rats producing blood lead levels comparable to those at which clinical signs of toxicity would be evident in humans results in a significant elevation in the incidence of kidney tumors.

Animal carcinogenesis studies conducted with lead and its compounds are numerous; however, with the exception of the study by Azar et al., (1973) they do not provide much useful information. Most of the studies shown in Table 12-18 were conducted with only one lead compound in one animal species, the rat. In cases where other lead compounds were tested or where other animal species were used, only a single high dosage level was administered, and parameters of toxicity such as those monitored in the Azar et al. (1973) study were not measured. Although it is clear from these studies as a whole that lead is a carcinogen in experimental

TABLE 12-19. MORTALITY AND KIDNEY TUMORS IN RATS FED LEAD ACETATE FOR TWO YEARS

Nominal (actual)[a] concentration in ppm of Pb in diet	No. of rats of each sex	% Mortality[b] Male	% Mortality[b] Female	% Kidney tumors Male	% Kidney tumors Female
0 (5)	100	37	34	0	0
10 (18)	50	36	30	0	0
50 (62)	50	36	28	0	0
100 (141)	50	36	28	0	0
500 (548)	50	52	36	10	0
0 (3)	20	50	35	0	0
1000 (1130)	20	50	50	50	0
2000 (2102)	20	80	35	80	35

[a]Measured concentration of lead in diet.

[b]Includes rats that either died or were sacrificed *in extremis*.

Source: Azar et al. (1973).

animals, until more investigations such as that of Azar et al. (1973) are conducted it is difficult to determine the relative carcinogenic potency of lead. There remains a need to test thoroughly the carcinogenic activity of lead compounds in experimental animals. These tests should include several modes of administration, many dosages spanning non-toxic as well as toxic levels, and several different lead compounds or at least a comparison of a relatively water-soluble form such as lead acetate with a less soluble form such as lead oxide.

12.7.2.3 *Cell Transformation*. Although cell transformation is an *in vitro* experimental system, its end point is a neoplastic change. There are two types of cell transformation assays: (1) those employing continuous cell lines, and (2) those employing cell cultures prepared from embryonic tissue. Use of continuous cell lines has the advantage of ease in preparation of the cell cultures, but these cells generally have some properties of a cancer cell. The absence of a few characteristics of a cancer cell in these continuous cell lines allows for an assay of cell transforming activity. End points include morphological transformation (ordered cell growth to disordered cell growth), ability to form colonies in soft agar-containing medium (a property characteristic of cancer cells), and ability of cells to form tumors when inoculated into experimental animals. Assays that utilize freshly isolated embryonic cells are generally preferred to those that use cell lines, because embryonic cells have not yet acquired any of the characteristics of a transformed cell. The cell transformation assay system has been utilized to examine the potential carcinogenic activity of a number of chemical agents, and the results seem to agree generally with the results of carcinogenesis

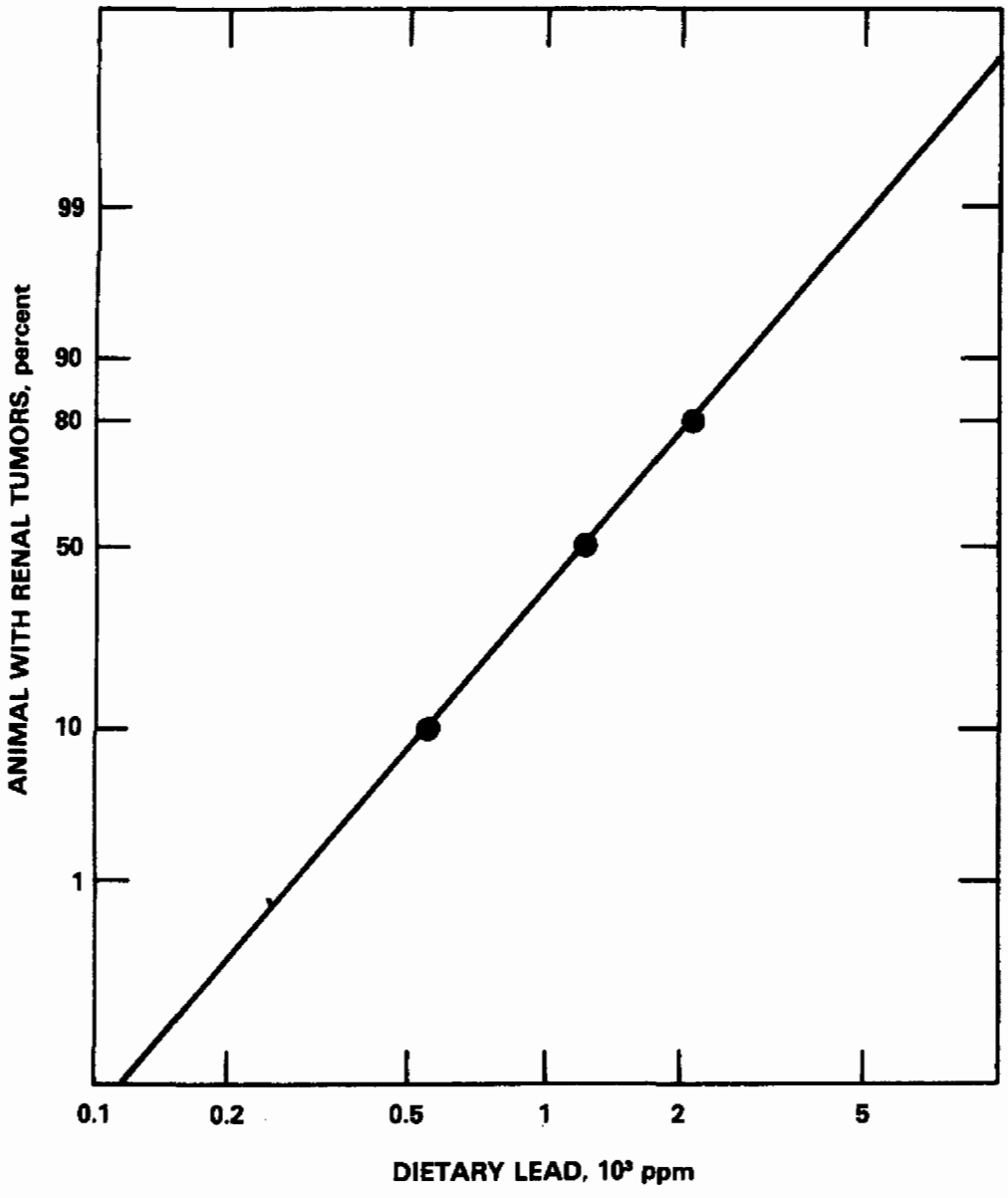

Figure 12-5. Probit plot of incidence of renal tumors in male rats.

Source: U.S. Environmental Protection Agency (1980) based on Azar et al. (1973).

tests using experimental animals. Cell transformation assays can be made quantitative by assessing the percentage of surviving colonies exhibiting morphological transformation. Verification of a neoplastic change can be accomplished by cloning these cells and testing their ability to form tumors in animals.

Lead acetate has been shown to induce morphological transformation in Syrian hamster embryo cells following a continuous exposure to 1 or 2.5 μg/ml of lead in culture medium for nine days (Dipaolo et al., 1978). The incidence of transformation increased from 0 percent in untreated cells to 2.0 and 6.0 percent of the surviving cells, respectively, following treatment with lead acetate. Morphologically transformed cells were capable of forming fibrosarcomas when cloned and administered to "nude" mice and Syrian hamsters, while no tumor growth resulted from similar inoculation with untreated cells (Dipaolo et al., 1978). In the same study lead acetate was shown to enhance the incidence of simian adenovirus (SA-7) induction of Syrian hamster embryo cell transformation. Lead acetate also caused significant enhancement (~2-3 fold) at 100 and 200 μg/ml following three hours of exposure. In another study (Casto et al., 1979), lead oxide also enhanced SA-7 transformation of Syrian hamster embryo cells almost 4 fold at 50 μM following three hours of exposure (Casto et al., 1979). The significance of enhanced virally induced carcinogenesis in relationship to the carcinogenic potential of an agent is not well understood.

Morphological transformation induced by lead acetate was correlated with the ability of the transformed cells to form tumors in appropriate hosts (see above), indicating that a truly neoplastic change occurred in tissue culture. The induction of neoplastic transformation by lead acetate suggests that this agent is potentially carcinogenic at the cellular level. However, with in vitro systems such as the cell transformation assay it is essential to compare the effects of other, similar types of carcinogenic agents in order to evaluate the response and to determine the reliability of the assay. The incidence of transformation obtained with lead acetate was greater than the incidence following similar exposure to $NiCl_2$, but less than that produced by $CaCrO_4$ (Heck and Costa, 1982a). Both nickel and chromium have been implicated in the etiology of human cancer (Costa, 1980). These results thus suggest that lead acetate has effects similar to those caused by other metal carcinogens. In particular, the ability of lead acetate to induce neoplastic transformation in cells in a concentration-dependent manner is highly suggestive of potential carcinogenic activity. It should also be noted that lead acetate induced these transformations at concentrations that decreased cell survival by only 27 percent (Heck and Costa, 1982a). Further studies from other laboratories utilizing the cell transformation assay and other lead compounds are needed.

12.7.3 Genotoxicity of Lead

Since cancer is known to be a disease of altered gene expression, numerous studies have evaluated changes in DNA consequent to exposure to suspected carcinogenic agents. The general response associated with such alterations in regulation of DNA function has been called genotoxicity. Various assay systems developed to examine specific changes in DNA structure and function caused by carcinogenic agents include assays that evaluate chromosomal aberrations, sister chromatid exchange, mutagenicity, and functional and structural features of DNA metabolism. Lead effects on these parameters are discussed below.

12.7.3.1 Chromosomal Aberrations. Two approaches have been used in the analysis of effects of lead on chromosomal structure. The first approach involves culturing lymphocytes either from humans exposed to lead or from experimental animals given a certain dosage of lead. The second approach involves exposing cultured lymphocytes directly to lead. For present purposes, emphasis will not be placed on the type of chromosomal aberration induced, since most of the available studies do not appear to associate any specific type of chromosomal aberration with lead exposure. It should be noted, however, that moderate aberrations include gaps and fragments, whereas severe aberrations include dicentric rings, translocations, and exchanges. Little is known of the significance of chromosomal aberrations in relationship to cancer, except that in a number of instances genetic diseases associated with chromosomal aberrations often enhance the probability of neoplastic disease. However, implicit in a morphologically distinct change in genetic structure is the possibility of an alteration in gene expression that represents a salient feature of neoplastic disease.

Contradictory reports exist regarding lead effects in inducing chromosomal aberrations (Tables 12-20 and 12-21). These studies have been grouped in two separate tables based upon their conclusions. Those studies reporting a positive effect of lead on chromosomal aberrations are indexed in Table 12-20, whereas studies reporting no association between lead exposure and chromosomal aberrations are indexed in Table 12-21. Unfortunately, these studies are difficult to evaluate fully because of many unknown variables (e.g., absence of sufficient evidence of lead intoxication, no dose-response relationship, and absence of information regarding lymphocyte culture time). To illustrate, in a number of the studies where lead exposure correlated with an increased incidence of chromosomal aberrations (Table 12-20), lymphocytes were cultured for 72 hours. Most cytogenetic studies have been conducted with a maximum culture time of 48 hours to avoid high background levels of chromosomal aberrations due to multiple cell divisions during culture. Therefore, it is possible that the positive effects of lead on chromosomal aberrations may have been due to the longer culture period. Nonetheless, it is evident that in the negative studies the blood lead concentration was generally lower than in the studies reporting a positive effect of lead on chromosomal aberrations, although in many of the latter instances blood lead levels indicated severe exposure.

TABLE 12-20. CYTOGENETIC INVESTIGATIONS OF CELLS FROM INDIVIDUALS EXPOSED TO LEAD: POSITIVE STUDIES

Number of exposed subjects	Number of controls	Cell culture time (hrs.)	Blood (µg/dl) or urine (µg/l) level	Exposed subjects	Type of damage	Remarks	References
8	14	?	62.-89. (blood)	Workers in a lead oxide factory	Chromatid and chromosome	Increase in chromosomal damage correlated with increased δ-ALA excretion	Schwanitz et al. (1970)
10	10	72	60.-100. (blood)	Workers in a chemical factory	Chromatid gaps, breaks	No correlation with blood lead levels	Gath & Thiess (1972)
14	5	48	155-720 (urine)	Workers in a zinc plant, exposed to fumes & dust of cadmium, zinc & lead	Gaps, fragments, exchanges, dicentrics, rings	Thought to be caused by lead, not cadmium or zinc	Deknudt et al. (1973)
105	-	72	11.6-97.4 mean, 37.7 (blood)	Blast-furnace workers, metal grinders, scrap metal processers	"Structural abnormalities," gaps, breaks, hyperploidy	No correlation with δ-ALA excretion or blood lead levels	Schwanitz et al. (1975)
11 (before and after exposure)	-	68-70	34.-64. (blood)	Workers in a lead-acid battery plant and a lead foundry	Gaps, breaks, fragments	No correlation with ALA-D activity in red cells	Forni et al. (1976)
44	15	72	30.-75. (blood)	Individuals in a lead oxide factory	Chromatid and chromosome aberrations	Positive correlation with length of exposure	Garza-Chapa et al. (1977)
23	20	48	44.-95. (not given)	Lead-acid battery melters, tin workers	Dicentrics, rings, fragments	Factors other than lead exposure may be required for severe aberrations	Deknudt et al. (1977b)
20	20	46-48	53.-100. (blood)	Ceramic, lead & battery workers	Breaks, fragments	Positive correlation with blood lead levels	Sarto et al. (1978)
26 (4 low, 16 medium, 6 high exposure)	not given	72	22.5-65. (blood)	Smelter workers	Gaps, chromatid and chromosome aberrations	Positive correlation with blood lead levels	Nordenson et al. (1978)
12	18	48-72	24-49 (blood)	Electrical storage battery workers	Chromatid and chromosome aberrations		Forni et al. (1980)

Source: International Agency for Research on Cancer (1980), with modifications.

TABLE 12-21. CYTOGENETIC INVESTIGATIONS OF CELLS FROM INDIVIDUALS EXPOSED TO LEAD: NEGATIVE STUDIES

Number of exposed subjects	Number of controls	Cell culture time (hrs.)	Blood lead level (μg/dl)	Exposed subjects	References
29	20	46-48	Not given, stated to be 20-30% higher than controls	Policemen "permanently in contact with high levels of automotive exhaust"	Bauchinger et al. (1972)
32	20	46-48	Range not given; highest level was 590 mg/l [sic]	Workers in lead manufacturing industry; 3 had acute lead intoxication	Schmid et al. (1972)
35	35	45-48	Control, <4.; exposed, 4. - >12.	Shipyard workers employed as "burners" cutting metal structures on ships	O'Riordan and Evans (1974)
24	15	48	19.3 (lead) 0.4 (cadmium)	Mixed exposure to zinc, lead, and cadmium in a zinc-smelting plant; significant increase in chromatid breaks and exchanges. Authors suggest that cadmium was the major cause of this damage	Bauchinger et al. (1976)
9	9	72	40.0 ± 5.0, 7 weeks	Volunteers ingested capsules containing lead acetate	Bulsma & De France (1976)
30	20	48	Control, 11.8-13.2; exposed, 29-33	Children living near a lead smelter	Bauchinger et al. (1977)

Source: International Agency for Research on Cancer (1980).

In some of these positive studies there was a correlation in the incidence of gaps, fragments, chromatid exchanges, and other chromosomal aberrations with blood lead levels (Sarto et al., 1978; Nordenson et al., 1978). However, as indicated in Table 12-20, in other studies there were no direct correlations between indices of lead exposure (i.e., δ-ALA excretion) and numbers of chromosomal aberrations. Nutritional factors such as Ca^{2+} levels *in vivo* or *in vitro* are also important since it is possible that the effects of lead on cells may be antagonized by Ca^{2+} (Mahaffey, 1983). As is usually the case in studies of human populations exposed to lead, exposure to other metals (zinc, cadmium, and copper) that may produce chromosomal aberrations was prevalent. None of the studies attempted to determine the specific lead compound that the individuals were exposed to.

In a more recent study by Forni et al. (1980), 18 healthy females occupationally exposed to lead were evaluated for chromosomal aberrations in their lymphocytes cultured for 48 or 72 hours. There were more aberrations at the 72-hour culture time compared with the 48-hour culture period in both control and lead-exposed groups, but this difference was not statistically significant. However, statistically significant differences from the 72-hour controls were noted in the 72-hour culture obtained from the lead exposed group. These results demonstrate that the extended 72-hour culture time results in increased chromosomal aberrations in the control lymphocytes and that the longer culture time was apparently necessary to detect the effects of lead on chromosomal structure. However, the blood lead levels in the exposed females ranged from 24 to 59 μg/dl, while control females had blood lead levels ranging from 22 to 37 μg/dl. Thus, there was a marginal effect of lead on chromosomal aberration, but the two groups may not have been sufficiently different in their lead exposure to show clear differences in frequency of chromosomal aberrations.

Some studies have also been conducted on the direct effect of soluble lead salts on cultured human lymphocytes. In a study by Beek and Obe (1974), longer (72-hr) culture time was used and lead acetate was found to induce chromosomal aberrations at 100 μM. Lead acetate had no effect on chromatid aberrations induced with X-rays or alkylating agents (Beek and Obe, 1975). In another study (Deknudt and Deminatti, 1978), lead acetate at 1 and 0.1 mM caused minimal chromosomal aberrations. Both cadmium chloride ($CdCl_2$) and zinc chloride ($ZnCl_2$) were more potent than lead acetate in causing these changes; however, both $CdCl_2$ and $ZnCl_2$ also displayed greater toxicity than lead acetate.

Chromosomal aberrations have been demonstrated in lymphocytes from cynomolgus monkeys treated chronically with lead acetate (6 mg/day, 6 days/week for 16 months), particularly when they were kept on a low calcium diet (Deknudt et al., 1977a). These aberrations accompanying a low Ca^{2+} diet were characterized by the authors as severe (chromatid exchanges, dispiralization, translocations, rings, and polycentric chromosomes). Similar results were observed in mice (Deknudt and Gerber, 1979). The effect of low calcium on chromosomal aberrations induced

by lead is most likely due to interaction of Ca^{2+} and Pb^{2+} at the level of the chromosome (Mahaffey, 1983). Léonard and his coworkers found no effect of lead on the incidence of chromosomal aberrations in accidentally intoxicated cattle (Léonard et al., 1974) or in mice given 1 gram of lead per liter of drinking water for 9 months (Léonard et al., 1973). However, Muro and Goyer (1969) found gaps and chromatid aberrations in bone marrow cells cultured for four days after isolation from mice that had been maintained on 1 percent dietary lead acetate for two weeks. Chromosomal loss has been reported (Ahlbert et al., 1972) in Drosophila exposed to triethyl lead (4 mg/l), but inorganic lead had no effect (Ramel, 1973). Lead acetate has also been shown to induce chromosomal aberrations in cultured cells other than lymphocytes, viz. Chinese hamster ovary cells (Bauchinger and Schmid, 1972).

These studies demonstrate that under certain conditions lead compounds are capable of inducing chromosomal aberrations in vivo and in tissue cultures. The ability of lead to induce these chromosomal changes appears to be concentration-dependent and highly influenced by calcium levels. In lymphocytes isolated from patients or experimental animals, relatively long (72-hr) culture conditions are required for the abnormalities to be expressed.

Sister chromatid exchange represents the normal movement of DNA in the genome. The sister chromatid exchange assay offers a very sensitive probe for the effects of genotoxic compounds on DNA rearrangement, as a number of chemicals with carcinogenic activity are capable of increasing these exchanges (Sandberg, 1982). The effect of lead on such movement has been examined in cultured lymphocytes (Beek and Obe, 1975), with no increase in exchanges observed at lead acetate concentrations of 0.01 mM. However, one study with lead at one dose in one system is not sufficient to rule out whether lead increases the incidence of these exchanges.

The ability of agents such as lead to cause abnormal rearrangements in the structure of DNA, as revealed by the appearance of chromosomal aberrations, and sister chromatid exchanges has become an important focus in carcinogenesis research. Current theories suggest that cancer may result from an abnormal expression of oncogenes (genes that code for protein products associated with virally induced cancers). Numerous oncogenes are found in normal human DNA, but the genes are regulated such that they are not expressed in an carcinogenic fashion. Rearrangement of these DNA sequences within the genome can lead to oncogenic expression. Evidence has been presented suggesting that chromosomal aberrations such as translocations are associated with certain forms of cancer and with the movement of oncogenes in regions of the DNA favoring their expression in cancer cells (Shen-Ong et al., 1982). By inducing aberrations in chromosomal structure, lead may enhance the probability of an oncogenic event.

12.7.3.2 Lead Effects on Bacterial and Mammalian Mutagenesis Systems. Bacterial and mammalian mutagenesis test systems examine the ability of chemical agents to induce changes in DNA sequences of a specific gene product that is monitored by selection procedures. They measure the potential of a chemical agent to produce a change in DNA, but this change is not likely to

be the same alteration in gene expression that occurs during oncogenesis. However, if an agent affects the expression of a particular gene product that is being monitored, then it could possibly affect other sequences which may result in cancer. Since many carcinogens are also mutagens, it is useful to employ such systems to evaluate genotoxic effects of lead.

Use of bacterial systems for assaying metal genotoxicity must await further development of bacterial strains that are appropriately responsive to known mutagenic metals (Rosenkranz and Poirier, 1979; Simmon, 1979; Simmon et al., 1979; Nishioka, 1975; Nestmann et al., 1979). Mammalian cell mutagenic systems that screen for specific alterations in a defined gene mutation have not been useful in detecting mutagenic activity with known carcinogenic metals (Heck and Costa, 1982b). In plants, however, chromosomal aberrations in root tips (Mukherji and Maitra, 1976) and other mutagenic activity, such as chlorophyll mutations (Reddy and Vaidyanath, 1978), have been demonstrated with lead.

12.7.3.3 Lead Effects on Parameters of DNA Structure and Function. There are a number of very sensitive techniques for examining the effect of metals on DNA structure and function in intact cells. Although these techniques have not been extensively utilized with respect to metal compounds, future research will probably be devoted to this area. Considerable work has been done to understand the effects of metals on enzymes involved in DNA transcription.

Sirover and Loeb (1976) examined effects of lead and other metal compounds upon the fidelity of transcription of DNA by a viral DNA polymerase. High concentrations of metal ions (in some cases in the millimolar range) were required to decrease the fidelity of transcription, but there was a good correlation between metal ions that are carcinogenic or mutagenic and their activity in decreasing the fidelity of transcription. This assay system measures the ability of a metal ion to incorporate incorrect (non-homologous) bases using a defined polynucleotide template. In an intact cell, this would cause the induction of a mutation if the insertion of an incorrect base is phenotypically expressed. Since the interaction of metal ions with cellular macromolecules is relatively unstable, misincorporation of a base during semi-conservative DNA replication or during DNA repair synthesis following breakage of DNA with a metal could alter the base sequence of DNA in an intact cell. Lead at 4 mM was among the metals listed as mutagenic or carcinogenic that caused a decrease in the fidelity of transcription (Sirover and Loeb, 1976). Other metals active in decreasing fidelity included: Ag^{+}, Be^{2+}, Cd^{2+}, Co^{2+}, Cr^{2+}, Cr^{3+}, Cu^{2+}, Mn^{2+}, and Ni^{2+}. No change in fidelity was produced by Al^{3+}, Ba^{2+}, Ca^{2+}, Fe^{3+}, K^{+}, Rb^{+}, Mg^{2+}, Mg^{+}, Se^{2+}, Sr^{2+}, and Zn^{2+}. Metals that decreased fidelity are metals also implicated as carcinogenic or mutagenic (Sirover and Loeb, 1976).

In a similar study, Hoffman and Niyogi (1977) demonstrated that lead chloride was the most potent of 10 metals tested in inhibiting RNA synthesis (i.e., $Pb^{2+} > Cd^{2+} > Co^{2+} > Mn^{2+} > Li^{+} > Na^{+} > K^{+}$) for both types of templates tested, i.e., calf thymus DNA and T_4 phage DNA.

These results were explained in terms of the binding of these metal ions more to the bases than to the phosphate groups of the DNA (i.e., $Pb^{2+} > Cd^{2+} > Zn^{2+} > Mn^{2+} > Mg^{2+} > Li^{+} = Na^{+} = K^{+}$). Additionally, metal compounds such as lead chloride with carcinogenic or mutagenic activity were found to stimulate mRNA chain initiation at 0.1 mM concentrations.

These well-conducted mechanistic studies provide evidence that lead can affect a molecular process associated with normal regulation of gene expression. Although far removed from the intact cell situation, these effects suggest that lead may be genotoxic.

12.7.4 Summary and Conclusions

It is evident from studies reviewed above that, at relatively high concentrations, lead displays some carcinogenic activity in experimental animals (e.g. the rat). An agent may act as a carcinogen in two distinct ways: (1) as an initiator or (2) as a promoter (Weisburger and Williams, 1980). By definition, an initiator must be able to interact with DNA to produce a genetic alteration, whereas a promoter acts in a way that allows the expression of an altered genetic change responsible for cancer. Since lead is capable of transforming cells directly in culture and affecting DNA-to-DNA and DNA-to-RNA transcription, it may have some initiating activity. Its ability to induce chromosomal aberrations is also indicative of initiating activity. There are no studies that implicate or support a promotional activity of lead; however, its similarity to Ca^{2+} suggests that it may alter regulation of this cation in processes (e.g., cell growth) related to promotion. Intranuclear lead inclusion bodies in the kidney may pertain to lead's carcinogenic effects, since both the formation of these bodies and the induction of tumors occur at relatively high doses of lead. The interaction of lead with key non-histone chromosomal proteins in the nucleus to form the inclusion bodies or the presence of inclusion bodies in the nucleus may alter genetic function, thus leading to cell transformation. Obviously, elucidating the mechanism of lead carcinogenesis requires further research efforts and only theories can be formulated regarding its oncogenic action at present.

It is hard to draw clear conlusions concerning what role lead may play in the induction of human neoplasia. Epidemiological studies of lead-exposed workers provide no definitive findings. However, statistically significant elevations in respiratory tract and digestive system cancer in workers exposed to lead and other agents warrant concern. Also, since lead acetate can produce renal tumors in some experimental animals, it may be prudent to assume that at least that lead compound may be carcinogenic in humans. However, this statement is qualified by noting that lead has been observed to increase tumorogenesis rates in animals only at relatively high concentrations, and therefore does not appear to be an extremely potent carcinogen. In vitro studies further support the genotoxic and carcinogenic role of lead, but also indicate that lead is not extremely potent in these systems either.

12.8 EFFECTS OF LEAD ON THE IMMUNE SYSTEM

12.8.1 Development and Organization of the Immune System

Component cells of the immune system arise from a pool of pluripotent stem cells in the yolk sack and liver of the developing fetus and in the bone marrow and spleen of the adult. Stem cell differentiation and maturation follows one of several lines to produce lymphocytes, macrophages, and polymorphonuclear leukocytes. These cells have important roles in immunological function and host defense.

The predominant lymphocyte class develops in the thymus, which is derived from the third and fourth pharyngeal pouches at 9 weeks of gestation in man (day 9 in mice). In the thymus microenvironment they acquire characteristics of thymus-derived lymphocytes (T-cells), then migrate to peripheral thymic-dependent areas of the spleen and lymph nodes. T-cells are easily distinguished from other lymphocytes by genetically defined cell surface markers that allow them to be further subdivided into immunoregulatory amplifier cells (helper T-cells) and suppressor T-cells that regulate immune responses. T-cells also participate directly as cytolytic effector cells against virally infected host cells, malignant cells, and foreign tissues as well as in delayed-type hypersensitivity (DTH) reactions where they elaborate lymphokines that modulate the inflammatory response. T-cells are long-lived lymphocytes and are not readily replaced. Thus, any loss or injury to T-cells may be detrimental to the host and result in increased susceptibility to viral, fungal, bacterial, or parasitic diseases. Individuals with acquired immune deficiency syndrome (AIDS) are examples of individuals with T-cell dysfunction. There is ample evidence that depletion by environmental agents of thymocytes or stem cell progenitors during lymphoid organogenesis can produce permanent immunosuppression.

The second major lymphocyte class differentiates from a lymphoid stem-cell in a yet undefined site in man, which would correspond functionally to the Bursa of Fabricius in avian species. In man, B-lymphocyte maturation and differentiation probably occur embryologically in gut-associated lymphoid tissue (GALT) and fetal liver, as well as adult spleen and bone marrow. This is followed by the peripheral population of thymic-independent areas of spleen and lymph nodes. Bone marrow-derived lymphocytes (B-cells), which mature independently of the thymus, possess specific immunoglobulin receptors on their surfaces. The presence of cell surface immunoglobulin (sIg) at high density is the major characteristic separating B-cells from T-cells. Following interaction with antigens and subsequent activation, B-lymphocytes proliferate and differentiate into antibody-producing plasma cells. In contrast to the long-lived T-cell, B-cells are rapidly replaced by newly differentiating stem cells. Therefore, lesions in the B-cell compartment may be less serious than those in the T-cell compartment since they are more easily reversed. Insult to B-cells at the stem cell or terminal maturation stage can result in suppression of specific immunoglobulin and enhanced susceptibility to infectious agents whose pathogenesis is limited by antibodies.

Pluripotent stem cells also give rise to lymphocytes whose lineages are still unclear. Some possess natural cytolytic activity for tumor cells (natural killer cell activity), while others, devoid of T- and B-cell surface markers (null cells), participate in antibody-dependent cell-mediated cytotoxicity (ADCC). The pluripotent stem cell pool also contains precursors of monocyte-macrophages and polymorphonuclear leukocytes (PMN). The macrophage has a major role in presentation and processing of certain antigens, in cytolysis of tumor target cells, and in phagocytosis and lysis of persistent intracellular infectious agents. Also, it actively phagocytizes and kills invading organisms. Defects in differentiation or function of PMNs or macrophages predispose the host to infections by bacteria and other agents.

This introduction should make it evident that the effects of an element such as lead on the immune system may be expressed in complex or subtle ways. In some cases, lead might produce a lesion of the immune system not resulting in markedly adverse health effects, especially if the lesion did not occur at an early stem cell stage or during a critical point in lymphoid organogenesis. On the other hand, some lead-induced immune system effects might adversely affect health through increasing susceptibility to infectious agents or neoplastically transformed cells if, for example, they were to impair cytocidal or bactericidal function.

12.8.2 Host Resistance

One way of ascertaining if a chemical affects the immune response of an animal is to challenge an exposed animal with a pathogen such as an infectious agent or oncogen. This provides a general approach to determine if the chemical interferes with host immune defense mechanisms. Host defense is a composite of innate immunity, part of which is phagocyte activities, and acquired immunity, which includes B- and T-lymphocyte and enhanced phagocyte reactivities. Analysis of host resistance constitutes a holistic approach. However, dependent on the choice of the pathogen, host resistance can be evaluated somewhat more selectively. Assessment of host resistance to extracellular microbes such as Staphylococci, Salmonella typhimurium, Escherichia coli, or Streptococcus pneumoniae and to intracellular organisms such as Listeria monocytogenes or Candida albicans primarily measures intact humoral immunity and cell-mediated immunity, respectively. Immune defense to extracellular organisms requires T-lymphocyte, B-lymphocyte, and macrophage interactions for the production of specific antibodies to activate the complement cascade and to aid phagocytosis. Antibodies can also directly neutralize some bacteria and viruses. Resistance to intracellular organisms requires T-lymphocyte and macrophage interactions for T-lymphocyte production of lymphokines, which further enhance immune mechanisms including macrophage bactericidal activities. An additional T-lymphocyte subset, the cytolytic T-cell, is involved in resistance to tumors; immune defenses against tumors are also aided by NK- and K-lymphocytes and macrophages.

12.8.2.1 Infectivity Models. Numerous studies designed to assess the influence of lead on host resistance to infectious agents consistently have shown that lead impairs host resistance, regardless of whether the defense mechanisms are predominantly dependent on humoral- or cell-mediated immunity (Table 12-22).

TABLE 12-22. EFFECT OF LEAD ON HOST RESISTANCE TO INFECTIOUS AGENTS

Species	Infectious agent	Lead dose	Lead exposure	Mortality[a]	Reference
Mouse	S. typhimurium	200 ppm	i.p.; 30 days	54% (13%)	Hemphill et al. (1971)
Rat	E. coli	2 mg/100 g	i.v.; 1 day	96% (0%)	Cook et al. (1975)
Rat	S. epidermidis	2 mg/100 g	i.v.; 1 day	80% (0%)	Cook et al. (1975)
Mouse	L. monocytogenes	80 ppm	orally; 4 wk	100% (0%)	Lawrence (1981a)
Mouse	EMC virus	2000 ppm	orally; 2 wk	100% (19%)	Gainer (1977b)
Mouse	EMC virus	13 ppm	orally; 10 wk	80% (50%)	Exon et al. (1979)
Mouse	Langat virus	50 mg/kg	orally; 2 wk	68% (0%)	Thind and Kahn (1978)

[a]The percent mortality is reported for the lowest dose of lead in the study that significantly altered host resistance. The percent mortality in parentheses is that of the non-lead-treated, infected control group.

Mice (Swiss Webster) injected i.p. for 30 days with 100 or 250 μg (per 0.5 ml) of lead nitrate and inoculated with Salmonella typhimurium had higher mortality (54 and 100 percent, respectively) than non-lead-injected mice (13 percent) (Hemphill et al., 1971). These concentrations of lead, by themselves, did not produce any apparent toxicity. Similar results were observed in rats acutely exposed to lead (one i.v. dose of 2 mg/100 g) and challenged with Escherichia coli (Cook et al., 1975). In these two studies, lead could have interfered with the clearance of endotoxin from the S. typhimurium or E. coli, and the animals may have died from endotoxin shock and not septicemia due to the lack of bacteriostatic or bactericidal activities. However, the study by Cook et al. (1975) also included a non-endotoxin-producing gram-positive bacterium, Staphylococcus epidermidis, and lead still impaired host resistance. In another study, lead effects on host resistance to the intracellular parasite Listeria monocytogenes were monitored (Lawrence, 1981a). CBA/J mice orally exposed to 16, 80, 400, and 2000 ppm lead for four weeks were assayed for viable Listeria after 48 and 72 hours, and for mortality after 10 days. Only 2000 ppm lead caused significant inhibition of early bactericidal activity (48-72 hr), but 80-2000 ppm lead produced 100 percent mortality, compared with 0 percent mortality in the 0-16 ppm lead groups. Other reports have suggested that host

resistance is impaired by lead exposure of rodents. Salaki et al. (1975) indicated that lead lowered resistance of mice to Staphylococcus aureus, Listeria, and Candida; and observed higher incidence of inflammation of the salivary glands in lead-exposed rats (Grant et al., 1980) may be due, in part, to lead-induced increased susceptibility to infections.

Inhalation of lead has also been reported to lower host resistance to bacteria. Schlipköter and Frieler (1979) exposed NMRI mice to an aerosol of 13-14 $\mu g/m^3$ lead chloride and clearance of Serratia marcesens in the lungs was reduced significantly. Microparticles of lead in lungs of mice were also shown to lower resistance to Pasteurella multocida, in that 6 µg of lead increased the percentage of mortality by 27 percent (Bouley et al., 1977).

Lead has also been shown to increase host susceptibility to viral infections. CD-1 mice, administered 2,000 and 10,000 ppm lead in drinking water for two weeks and subsequently inoculated with encephalomyocarditis (EMC) virus, had a significant increase in mortality (100 percent at 2,000 ppm; 65 percent at 10,000 ppm) compared with control EMC virus-infected mice (13 percent) (Gainer, 1977b). In another study (Exon et al., 1979), Swiss Webster mice were exposed to 13, 130, 1300, or 2600 ppm lead for 10 weeks in their drinking water and were infected with EMC virus. Although as low as 13 ppm lead caused a significant increase in mortality (80 percent) in comparison with the non-lead-treated EMC virus-infected mice (50 percent), there were no dose-response effects, in that 2600 ppm lead resulted in only 64 percent mortality. The lack of a dose-response relationship in the two studies with EMC virus (Gainer, 1977b; Exon et al., 1979) suggests that the higher doses of lead may directly inhibit EMC infectivity as well as host defense mechanisms. Additional studies have confirmed that lead inhibits host resistance to viruses. Mice treated orally with lead nitrate (10-50 mg/kg/ day) for two weeks had suppressed antibody titers to Langat virus (Type B arbovirus) and increased titers of the virus itself (Thind and Singh, 1977), and the lead-inoculated, infected mice had higher mortalities (25 percent at 10 mg/kg; 68 percent at 50 mg/kg) than the non-lead-infected mice (0 percent) (Thind and Khan, 1978).

The effects of lead on bacterial and viral infections in humans have never been studied adequately; there is only suggestive evidence that human host resistance may be lowered by lead. Children with persistently high blood lead levels who were infected with Shigella enteritis had prolonged diarrhea (Sachs, 1978). In addition, lead workers with blood lead levels of 22-89 µg/dl have been reported to have more colds and influenza infections per year (Ewers et al., 1982). This study also indicated that secretory IgA levels were suppressed significantly in lead workers with a median blood lead level of 55 µg/dl. Secretory IgA is a major factor in immune defense against respiratory as well as gastrointestinal infections.

Hicks (1972) points out that there is need for systematic epidemiological studies on the effects of elevated lead levels on the incidence of infectious diseases in humans. The current paucity of information precludes formulation of any clear dose-response relationship for

humans. Epidemiological investigations may help to determine if lead alters the immune system of man and consequently increases susceptibility to infectious agents and neoplasia.

12.8.2.2 Tumor Models and Neoplasia. The carcinogenicity of lead has been studied both as a direct toxic effect of lead (see Section 12.7) and as a means of better understanding the effects of lead on the body's defense mechanisms. Studies by Gainer (1973, 1974) demonstrated that exposure of CD-1 mice to lead acetate potentiated the oncogenicity of a challenge with Rauscher leukemia virus (RLV), resulting in enhanced splenomegaly and higher virus titers in the spleen presumably through an immunosuppressive mechanism. Recent studies by Kerkvliet and Baecher-Steppan (1982) revealed that chronic exposure of C57BL/6 mice to lead acetate in drinking water at 130-1300 ppm enhanced the growth of primary tumors induced by Moloney sarcoma virus (MSV). Regression of MSV-induced tumors was not prevented by lead exposure, and lead-treated animals resisted late sarcoma development following primary tumor resistance. Depressed resistance to transplantable MSV tumors was associated with a reduced number of macrophages, which also exhibited reduced phagocytic activity.

In addition to enhancing the transplantability of tumors or the oncogenicity of leukemia viruses, lead has also been shown to facilitate the development of chemically induced tumors. Kobayashi and Okamoto (1974) found that intratracheal dosing of benzo(a)pyrene (BaP) combined with lead oxide resulted in an increased frequency of lung adenomas and adenocarcinomas over mice exposed to BaP alone. Similarly, exposure to lead acetate enhanced the formation of N(4'-fluoro-4-biphenyl) acetamide-induced renal carcinomas from 70 to 100 percent and reduced the latency to tumor appearance (Hinton et al., 1980). Recently, Koller et al. (1983) found that exposure to lead for 18 months increased the frequency of spontaneous tumors, predominantly renal carcinomas, in rats. Similarly, Schrauzer et al. (1981) found that adding lead at 5 ppm to drinking water of C3H/St mice infected with Bittner milk factor diminished the uptake of selenium and reduced its anticarcinogenic effects, causing mammary tumors to appear at the same high incidence as in selenium-unsupplemented controls. Lead likewise significantly accelerated tumor growth and shortened survival in this model.

The above studies on host susceptibility to various pathogens, including infectious agents and tumors, indicate that lead could be detrimental to health by methods other than direct toxicity. In order to understand the mechanisms by which lead suppresses host resistance maintained by phagocytes, humoral immunity, and/or cell-mediated immunity, the immune system must be dissected into its functional components and the effects of lead on each, separately and combined, must be examined in order that the mechanism(s) of the immunomodulatory potential of lead can be understood.

12.8.3 Humoral Immunity

12.8.3.1 Antibody Titers. A low antibody titer in animals exposed to lead could explain the increased susceptibility of animals to extracellular bacteria and some viruses (see Table

12-23), as well as to endotoxins (Selye et al., 1966; Filkins, 1970; Cook et al., 1974; Schumer and Erve, 1973; Rippe and Berry, 1973; Truscott, 1970). Specific antibodies can directly neutralize pathogens, activate complement components to induce lysis, or directly or indirectly enhance phagocytosis via Fc receptors or C3 receptors, respectively. Studies in animals and humans have assayed the effects of lead on serum immunoglobulin levels, specific antibody levels, and complement levels. Analysis of serum immunoglobulin levels is not a good measure of specific immune reactivity, but it would provide evidence for an effect on B-lymphocyte development.

TABLE 12-23. EFFECT ON LEAD ON ANTIBODY TITERS

Species	Antigen	Lead dose and exposure	Effect	Reference
Rabbit	Pseudorabies virus	2500 ppm; 10 wk	Decrease	Koller (1973)
Rat	S. typhimurium	5000-20000 ppm; 3 wk	Decrease	Stanković and Jugo (1976)
Rat	Bovine serum albumin	10-1000 ppm; 10 wk	Decrease	Koller et al. (1983)
Mouse	Sheep red blood cells	0.5-10 ppm[a]; 3 wk	Decrease	Blakley et al. (1980)

[a]Lead was administered as tetraethyl lead; other studies used inorganic forms.

Lead had little effect on the serum immunoglobulin levels in rabbits (Fonzi et al., 1967a), children with blood lead levels of 40 µg/dl (Reigart and Garber, 1976), or lead workers with 22-89 µg/dl (Ewers et al., 1982). On the other hand, most studies have shown that lead significantly impairs antibody production. Acute oral lead exposure (50,000 ppm/kg) produced a decreased titer of anti-typhus antibodies in rabbits immunized with Typhus vaccine (Fonzi et al., 1967b). In New Zealand white rabbits challenged with pseudorabies virus, lead (oral exposure to 2500 ppm for 70 days) caused a 9-fold decrease in antibody titer to the virus (Koller, 1973). However, lead has not always been shown to reduce titers to virus. Vengris and Mare (1974) did not observe depressed antibody titers to Newcastle disease virus in lead-treated chickens, but their lead treatment was only for 35 days prior to infection. Lead-poisoned children also had normal anti-toxoid titers after booster immunizations with tetanus toxoid (Reigart and Garber, 1976). In another study, Wistar rat dams were exposed to 5,000, 10,000, or 20,000 ppm lead for 20 days following parturition (Stanković and Jugo, 1976). The progeny were weaned at 21 days of age and given standard laboratory chow for an

additional month. At that time, they were injected with Salmonella typhimurium, and serum antibody titers were assessed. Each dosage of lead resulted in significantly reduced antibody titers. More recently, rats (Sprague-Dawley) given 10 ppm lead acetate orally for 10 weeks had a significant suppression in antibody titers when challenged with bovine serum albumin (BSA) and compared with BSA-immunized non-lead-exposed rats (Koller et al., 1983). Development of a highly sensitive, quantitative, enzyme-linked immunosorbent assay (ELISA) contributed to detecting the immunosuppressive activity of lead at this dosage.

Tetraethyl lead also has been responsible for reduced antibody titers in Swiss-cross mice (Blakley et al., 1980). The mice were exposed orally to 0.5, 1.0, and 2.0 ppm tetraethyl lead for 3 weeks. A significant reduction in hemagglutination titers to sheep red blood cells (SRBC) occurred at all levels of exposure.

12.8.3.2 Enumeration of Antibody Producing Cells (Plaque-Forming Cells). From the above results, it appears that lead inhibits antibody production. To evaluate this possible effect at the cellular level, the influence of lead on the number of antibody producing cells after primary or secondary immunization can be assessed. In primary humoral immune responses (mostly direct), IgM plaque-forming cells (PFC) are measured, whereas in secondary or anamnestic responses (mostly indirect), IgG PFC are counted. The primary immune response represents an individual's first contact with a particular antigen. The secondary immune response represents re-exposure to the same antigen weeks, months, or even years after the primary antibody response has subsided. The secondary immune response is attributed to persistence, after initial contact with the antigen, of a substantial number of antigen-sensitive memory cells. Impairment of the memory response, therefore, results in serious impairment of humoral immunity in the host.

Table 12-24 summarizes the effects of lead on IgM or IgG PFC development. Mice exposed orally to tetraethyl lead (0.5, 1, or 2 ppm) for three weeks produced a significant reduction in the development of IgM and IgG PFC (Blakley et al., 1980). Mice (Swiss Webster) exposed orally to 13, 137, or 1375 ppm inorganic lead for eight weeks had reduced numbers of IgM PFC in each lead-exposed group (Koller and Kovacic, 1974). Even the lowest lead group (13 ppm) had a decrease. The secondary response (IgG PFC, induced by a second exposure to antigen SRBC seven days after the primary immunization) was inhibited to a greater extent than the primary response. This study indicated that chronic exposure to lead produced a significant decrease in the development of IgM PFC and IgG PFC. When Swiss Webster mice were exposed to 13, 130, and 1300 ppm lead for 10 weeks and hyperimmunized by SRBC injections at week 1, 2, and 9, the memory response as assessed by the enumeration of IgG PFC was significantly inhibited at 1300 ppm (Koller and Roan, 1980a). This suggests that the temporal relationships between lead exposure and antigenic challenge may be critical. Other studies support this interpretation.

TABLE 12-24. EFFECT OF LEAD ON THE DEVELOPMENT OF ANTIBODY-PRODUCING CELLS (PFC)

Species	Antigen[a]	Lead dose and exposure	Effect[b]	Reference
Mouse	SRBC (in vivo)	13-1370 ppm; 8 wk	IgM PFC (D) IgG PFC (D)	Koller and Kovacic (1974)
Mouse	SRBC (in vivo)	0.5-2 ppm tetraethyl lead; 3 wk	IgM PFC (D) IgG PFC (D)	Blakley et al. (1980)
Mouse	SRBC (in vivo)	13-1370 ppm; 10 wk	IgG PFC (D)	Koller and Roan (1980a)
Mouse	SRBC (in vivo)	4 mg (i.p. or orally)	IgM PFC (I) IgG PFC (D)	Koller et al. (1976)
Mouse	SRBC (in vivo) SRBC (in vitro + 2-ME)	16-2000 ppm; 1-10 wk 16-80 ppm; 4 wk 2000 ppm; 4 wk	IgM PFC (N) IgM PFC (I) IgM PFC (D)	Lawrence (1981a)
Rat	SRBC (in vivo)	25-50 ppm; pre/postnatal	IgM PFC (D)	Luster et al. (1978)
Mouse	SRBC (in vitro) SRBC (in vitro + 2-ME)	50-1000 ppm; 3 wk 50-1000 ppm; 3 wk	IgM PFC (D) IgM PFC (N or I)	Blakley and Archer (1981)
Mouse	SRBC (in vitro + 2-ME)	2-20 ppm (in vitro)	IgM PFC (I)	Lawrence (1981b,c)

[a]The antigenic challenge with sheep red blood cells (SRBC) was in vivo or in vitro after in vivo exposure to lead unless otherwise stated. The in vitro assays were performed in the presence or absence of 2-mercaptoethanol (2-ME).

[b]The letters in parentheses are defined as follows: D = decreased response; N = unaltered response; I = increased response.

Female Sprague-Dawley rats with pre- and post-natal exposure to lead (25 or 50 ppm) had a significant reduction in IgM PFC (Luster et al., 1978). In contrast, CBA/J mice exposed orally to 16-2000 ppm lead for 1-10 weeks did not have altered IgM PFC responses to SRBC (Lawrence, 1981a). Furthermore, when Swiss Webster mice were exposed to an acute lead dose (4 mg lead orally or i.p.), the number of IgG PFC was suppressed, but the number of IgM PFC was enhanced (Koller et al., 1976).

The influence of lead on the development of PFC in mice was assessed further by in vivo exposure to lead, removal of spleen cells, and in vitro analysis of PFC development. Initially it appeared that low doses of lead (16 and 80 ppm) enhanced development, and only a high

dose (2000 ppm) inhibited the development of IgM PFC (Lawrence, 1981a). However, a later study by Blakley and Archer (1981) indicated that 50-1000 ppm lead consistently inhibited IgM PFC. Through the analysis of mixed cultures of lead-exposed lymphocytes (nonadherent cells) and unexposed macrophages (adherent cells), and vice versa, as well as of in vitro responses to antigens that do not require macrophage help (i.e., lipopolysaccharide, LPS), their data indicated that the effects of lead may be at the level of the macrophage. This was substantiated by the fact that 2-mercaptoethanol (2-ME, a compound that can substitute for at least one macrophage activity) was able to reverse the inhibition by lead. This may explain why in vivo lead exposure (16 and 80 ppm) appeared to enhance the in vitro IgM PFC responses in the study by Lawrence (1981a), because 2-ME was present in the in vitro assay system. Furthermore, in vitro exposure to lead (2 or 20 ppm) in spleen cell cultures with 2-ME enhanced the development of IgM PFC (Lawrence, 1981b,c).

These experiments indicate that lead modulates the development of antibody-producing cells as well as serum antibody titers, which supports the notion that lead can suppress humoral immunity. However, it should be noted that the dose and route of exposure of both lead and antigen may influence the modulatory effects of lead. The adverse effects of lead on humoral immunity may be due more to lead's interference with macrophage antigen processing and/or antigen presentation to lymphocytes than to direct effects on B-lymphocytes. These mechanisms require further investigation.

12.8.4 Cell-Mediated Immunity

12.8.4.1 Delayed-Type Hypersensitivity. T-lymphocytes (T-helper and T-suppressor cells) are regulators of humoral and cell-mediated immunity as well as effectors of two aspects of cell-mediated immunity. T-cells responsive to delayed-type hypersensitivity (DTH) produce lymphokines that induce mononuclear infiltrates and activate macrophages, which are aspects of chronic inflammatory responses. In addition, another subset of T-cells, cytolytic T-cells, cause direct lysis of target cells (tumors or antigenically modified autologous cells) when in contact with the target. To date, the effects of lead on cytolytic T-cell reactivity have not been measured, but the influence of lead on inducer T-cells has been studied (Table 12-25). Groups of mice injected i.p. daily for 30 days with 13.7 to 137 ppm lead were subsequently sensitized i.v. with SRBC. The DTH reaction was suppressed in these animals in a dose-related fashion (Müller et al., 1977). The secondary DTH response was inhibited in a similar fashion. In another study (Faith et al., 1979), the effects of chronic low level pre- and post-natal lead exposure on cellular immune functions in Sprague-Dawley rats was assessed. Female rats were exposed to 25 or 50 ppm lead acetate continuously for seven weeks before breeding and through gestation and lactation. The progeny were weaned at three weeks of age and continued on the respective lead exposure regimen of their mothers for an additional 14 to 24 days.

TABLE 12-25. EFFECT OF LEAD ON CELL-MEDIATED IMMUNITY

Species	Lead dose and exposure	Parameter*	Effect	Reference
Mouse	13.7-137 ppm; 4 wk	DTH	Decrease	Müller et al. (1977)
Rat	25-50 ppm; 8 wk	DTH	Decrease	Faith et al. (1979)
Mouse	13-1300 ppm; 10 wk	MLC	None	Koller and Roan (1980b)
Mouse	16-2000 ppm; 4 wk	MLC	Decrease	Lawrence (1981a)

*DTH =delayed-type hypersensitivity; MLC = mixed lymphocyte culture.

Thymic weights and DTH responses were significantly decreased by both lead dosages. These results indicate that chronic low levels of lead suppress cell-mediated immune function.

The in vitro correlate of the analysis of DTH responsive T-cells in vivo is the analysis of mixed lymphocyte culture (MLC) responsive T-cells. When two populations of allogeneic lymphoid cells are cultured together, cellular interactions provoke blast cell transformation and proliferation of a portion of the cultured cells (Cerottini and Brunner, 1974; Bach et al., 1976). The response can be made one-way by irradiating one of the two allogeneic preparations, in which case the irradiated cells are the stimulators (allogeneic B-cells and macrophages) and the responders (T-cells) are assayed for their proliferation. The mixed lymphocyte reaction is an in vitro assay of cell-mediated immunity analogous to in vivo host versus graft reactions.

Mice (DBA/2J) fed 13, 130, or 1300 ppm lead for 10 weeks were evaluated for responsiveness in mixed lymphocyte cultures. The 130-ppm lead dose tended to stimulate the lymphocyte reaction, although no change was observed at the other dose levels (Koller and Roan, 1980b). In another study (Lawrence, 1981a), mice (CBA/J) were fed 16, 80, 400, or 2000 ppm lead for four weeks. The 16 and 80 ppm doses slightly stimulated, while the 2000 ppm dose suppressed, the mixed lymphocyte reaction. It is important to note that in these in vitro MLC assays, 2-ME was present in the culture medium, and the 2-ME may have reversed the in vivo effects of lead, as was observed for the in vitro PFC responses (Blakley and Archer, 1981).

The data on the effects of lead on humoral and cell-mediated immunity indicate that in vivo lead usually is immunosuppressive, but additional studies are necessary to fully understand the temporal and dose relationship of lead's immunomodulatory effects. The in vitro analysis of immune cells exposed to lead in vivo suggest that the major cell type modified is the macrophage; the suppressive effects of lead may be readily reversed by thiol reagents possibly acting as chelators.

12.8.4.3 Interferon. Interferons (IF) are a family of low molecular weight proteins which exhibit antiviral activity in sensitive cells through processes requiring new cellular RNA and protein synthesis (Stewart, 1979). It has been speculated that the enhanced susceptibility of lead-treated mice to infectious virus challenge might be due to a decreased capacity of these animals to produce viral or immune interferons or to respond to them. Studies by Gainer (1974, 1977a) appeared to resolve this question and indicated that exposure of CD-1 mice to lead does not inhibit the antiviral action of viral IF in vivo or in vitro. In the later of the two studies, lead exposure inhibited the protective effects of the IF inducers Newcastle disease virus and poly I:poly C against encephalomyocarditis virus (EMC)-induced mortality. These data suggest that, although lead did not directly interfere with the antiviral activity of interferon, it might suppress viral IF production in vivo. Recently, Blakley et al. (1982) re-examined this issue and found that female BDF_1 mice exposed to lead acetate in drinking water at concentrations ranging from 50 to 1000 µg/ml for three weeks produced amounts of IF similar to controls given a viral IF inducer, Tilorone. Similarly, the in vitro induction of immune IF by the T-cell mitogens phytohemagglutinin, concanavalin A, and staphylococcal enterotoxin in lymphocytes from lead-exposed mice were unaltered compared with controls (Blakley et al., 1982). Thus, lead exposure does not appear to significantly alter the lymphocyte's ability to produce immune interferon. Therefore, it must be assumed that increased viral susceptibility associated with chronic lead exposure in rodents is by mechanisms other than interference with production of or response to interferon.

12.8.5 Lymphocyte Activation by Mitogens

Mitogens are lectins that induce activation, blast-cell transformation, and proliferation in resting lymphocytes. Certain lectins bind specifically to (1) T-cells (i.e., phytohemagglutinin [PHA] and concanavalin A [Con A]), (2) B-cells (i.e., lipopolysaccharide [LPS] of gram-negative bacteria) or (3) both (i.e., pokeweed mitogen [PWM]). The blastogenic response produced can be used to assess changes in cell division of T- and B-lymphocytes. The biological significance of the following studies is difficult to interpret since exposure to lead was either in vivo or in vitro at different doses and for different exposure periods.

12.8.5.1 In Vivo Exposure. Splenic lymphocytes from Swiss Webster mice exposed orally to 2000 ppm lead for 30 days had significantly depressed proliferative responses to PHA (Table 12-26) which were not observed after 15 days of exposure (Gaworski and Sharma, 1978). Suppression was likewise observed with PWM, a T- and B-cell mitogen. These observations with T-cell mitogens were confirmed in Sprague-Dawley rats exposed orally to 25 or 50 ppm lead pre- and postnatally for seven weeks (Faith et al., 1979). Splenic T-cell responses to Con A and PHA were significantly diminished. A similar depression of Con A and PHA responses occurred

TABLE 12-26. EFFECT OF LEAD EXPOSURE ON MITOGEN ACTIVATION OF LYMPHOCYTES

Species	Lead dose	Mitogen	Effect	Reference
Mice	In vivo, 250 and 2000 ppm, 30 days	PHA (T-Cell)	Significantly depressed at 2000 ppm on day 30 only[1]	Gaworski and Sharma (1978)
		PWM (T and B-Cell)	Significantly depressed at 2000 ppm on both days 15 and 30[1]	
Mice	In vivo, 13, 130 and 1300 ppm, 10 weeks	Con A (T-Cell)	No effect	Koller et al. (1979)
		LPS (B-Cell)	No effect	
Rats	In vivo, pre/postnatal 25 and 50 ppm, 7 weeks	Con A	Significantly depressed at 25 and 50 ppm	Faith et al. (1979)
		PHA	Significantly depressed at 50 ppm only	
Mice	In vivo, .08 - 10 mM, 4 weeks	Con A, PHA	No effect	Lawrence (1981c)
		LPS	Depressed at 2 and 10 mM	
Mice	In vivo, 1300 ppm, 8 weeks	Con A, PHA	Significantly depressed	Neilan et al. (1980)
		LPS	No effect	
Mice	In vivo, 50, 200 and 1000 ppm 3 weeks	Con A, PHA, SEA	Increased to all[2]	Blakley and Archer (1982)
		LPS	No effect	
Mice	In vitro, 10^{-4} - 10^{-6} for full culture period	Con A, PHA	Slightly increased at highest dose at day 2, no effect at day 3.5	Lawrence (1981a,b)
		LPS	Increased up to 245%[1]	
Mice	In vitro, 0.1, 0.5, 1.0 mM for full culture period	PHA	Increased at all doses by up to 453%[3]	Gaworski and Sharma (1978)
		PWM	Increased by approximately 250% at 0.1 and 0.5 mM only	
Mice	In vitro, 10^{-3} - 10^{-7} M	LPS	Increased by up to 312%	Shenker et al. (1977) Gallagher et al. (1979)

1. Difficult to interpret since data were reported only as % of control response rather than CPM of ^{3}H-TdR incorporation.
2. Untreated control values unusually low for T-cell response. Lead treated had much higher response with highest dose showing cytotoxicity.
3. Noted white precipitate thought to be lead carbonate in cultures.

in lymphocytes from C57B1/6 mice exposed to 1300 ppm lead for 8 weeks (Neilan et al., 1980). Lead impaired blastogenic transformation of lymphocytes by both T-cell mitogens, although the B-cell proliferative response to LPS was not impaired.

In contrast to reports that lead exposure suppressed the blastogenic response of T-cells to mitogens, several laboratories have reported that lead exposure does not suppress T-cell proliferative responses (Koller et al., 1979; Lawrence, 1981c; Blakley and Archer, 1982). These differences are not easily reconciled since analysis of the lead dose employed and exposure period (Table 12-25) provides little insight into the observed differences in T-cell responses. In one case, a dose of 2000 ppm for 30 days produced a clear depression while a lesser dose of 1300 ppm produced no effect at 10 weeks in another laboratory. These data are confusing and may reflect technical differences in performing the T-cell blastogenesis assay in different laboratories, a lack of careful attention to lectin response kinetics, or the influence of suppressor macrophages. Thus, no firm conclusion can be drawn regarding the ability of in vivo exposure to lead to impair the proliferative capacity of T-cells.

The blastogenic response of B-cells to LPS was unaffected in four different in vivo studies at lead exposure levels from 25 to 1300 ppm (Koller et al., 1979; Faith et al., 1979; Neilan et al., 1980; Blakley and Archer, 1982). Lawrence (1981c), however, reported that the LPS response was suppressed after 4 weeks exposure at 2 and 10 mM lead. The weight of the data suggests that the proliferative response of B-cells to LPS is probably not severely impaired by lead exposure.

12.8.5.2 In Vitro Exposure. The biological relevance of immunological studies in which lead was added in vitro to normal rodent splenocytes in the presence of a mitogen (Table 12-26) is questionable since differences probably reflect either a direct toxic or stimulatory effect by the metal. These models may, however, provide useful information regarding metabolic and functional responses in lymphocytes using lead as a probe.

In one study, lymphocytes were cultured in the presence of lead (10^{-4}, 10^{-5}, and 10^{-6} M). A slight but significant increase in lymphocyte transformation occurred on day 2 at the highest lead dosage when stimulated with Con A or PHA (Lawrence, 1981b). In a follow-up study where the kinetics of the lectin response were examined (Lawrence, 1981a), lead (10^{-4}, 10^{-5}, and 10^{-6} M) significantly suppressed the Con A- and PHA-induced proliferative responses of lymphocytes on day 2, but not on days 3 to 5. In yet another in vitro exposure study, lymphocytes cultured in the presence of 0.1, 0.5, or 1.0 mM lead had a significantly enhanced response to PHA (Gaworski and Sharma, 1978). It should be kept in mind when considering these in vitro exposure observations that lead has been demonstrated to be directly mitogenic to lymphocytes (Shenker et al., 1977). The data discussed here suggest that lead may also be slightly co-mitogenic with T-cell mitogens. Direct exposure of lymphocytes in culture to lead can also result in decreased lymphocyte viability (Gallagher et al., 1979). In vitro studies

on the effect of lead on the B-cell blastogenic response to LPS indicated that lead is potently co-mitogenic with LPS and enhanced the proliferative response of B-cells by 245 percent (Lawrence 1981b,c) to 312 percent (Shenker et al., 1977; Gallagher et al., 1979).

12.8.6 Macrophage Function

The monocyte/macrophage is involved with phagocytosis, bactericidal activity, processing of complex antigens for initiation of antibody production, interferon production, endotoxin detoxification, and immunoregulation. Since some of these functions are altered in lead-treated rodents (Table 12-27), the monocyte/macrophage or comparable phagocytic cell in the liver has been suggested as a possible cellular target for lead (Trejo et al., 1972; Cook et al., 1974; Müller et al., 1977; Luster et al., 1978; Blakley and Archer, 1981).

Several laboratories have shown that a single i.v. injection of lead impaired the phagocytic ability of the reticuloendothelial system (RES) (Trejo et al., 1972; Cook et al., 1974; Filkins and Buchanan, 1973). Trejo et al. (1972) found that an i.v. injection of 5 mg lead impaired vascular clearance of colloidal carbon that resulted from an impaired phagocytic ability of liver Kupffer cells. Similarly, others have confirmed that lead injected i.v. depressed intravascular clearance of colloidal carbon (Filkins and Buchanan, 1973) as well as a radiolabeled lipid emulsion (Cook et al., 1974). Opposite effects on RES function have been seen when lead was given orally (Koller and Roan, 1977). Similarly, Schlick and Friedberg (1981) noted that a 10-day exposure to 10-1000 µg lead enhanced RES clearance and endotoxin hypersensitivity.

Lead has likewise been demonstrated to suppress macrophage-dependent immune responses (Blakley and Archer, 1981). Exposure of BDF_1 mice to lead (50 ppm) for three weeks in drinking water suppressed *in vitro* antibody PFC responses to the macrophage-dependent antigens, sheep red blood cells or dinitrophenyl-Ficoll, but not to the macrophage-independent antigen *E. coli* lipopolysaccharide. The macrophage substitute 2-mercaptoethanol and macrophages from non-exposed mice restored lead-suppressed response. Castranova et al. (1980) found that cultured rat alveolar macrophages exposed to lead had depressed oxidative metabolism.

The effects of heavy metals on endotoxin hypersensitivity were first observed by Selye et al. (1966), who described a 100,000-fold increase in bacterial endotoxin sensitivity in rats given lead acetate. The increased sensitivity to endotoxin was postulated to be due to a blockade of the RES. Filkins (1970) subsequently demonstrated that endotoxin detoxification is primarily a hepatic macrophage-mediated event that is profoundly impaired by lead exposure (Trejo and Di Luzio, 1971; Filkins and Buchanan, 1973). The several types of data described above suggest that macrophage dysfunction may be contributing to impairment of immune function, endotoxin detoxification, and host resistance following lead exposure.

TABLE 12-27. EFFECT OF LEAD ON MACROPHAGE AND RETICULOENDOTHELIAL SYSTEM FUNCTION

Species	Lead dose and exposure	Parameter	Effect	Reference
Rat	2.25 µmol i.v., single injection	Vascular clearance; lipid emulsion endotoxin sensitivity	Depressed Increased	Cook et al. (1974); Trejo et al. (1972)
Rat	5 mg i.v., single injection	Vascular clearance; colloidal carbon endotoxin sensitivity	Depressed Increased	Trejo et al. (1972); Filkins and Buchanan (1973)
Mouse	13, 130, 1300 ppm oral, 10-12 weeks	Phagocytosis	Depressed	Kervliet and Braecher-Steppan (1982)
Guinea Pig	10^{-3}-10^{-6} M	Macrophage migration	Depressed	Kiremidjian-Schumacher et al. (1981)
Rat	10^{-3}-10^{-6} M	Macrophage oxygen metabolism	Depressed	Castranova et al. (1980)
Mouse	50-1000 ppm oral, 3 weeks	Macrophage dependent antigens PFC response	Depressed	Blakley and Archer (1981)
Mouse	10-1000 µg, 10 days	Vascular clearance	Enhanced at 10 days; no effect at >30 days.	Schlick and Friedberg (1981)
		Endotoxin sensitivity	Increased	

12.8.7 Mechanisms of Lead Immunomodulation

The mechanism of toxic action of lead on cells is complex (see Section 12.2). Since lead has a high affinity for sulfhydryl groups, a likely subcellular alteration accounting for the immunomodulatory effects of lead on immune cells is its association with cellular thiols. Numerous studies have indicated that surface and intracellular thiols are involved in lymphocyte activation, growth, and differentiation. Furthermore, the study by Blakley and Archer (1981) suggests that lead may inhibit the macrophage's presentation of stimulatory products to the lymphocytes. This process may rely on cellular thiols since the inhibitory effects of lead can be overcome by an exogenous thiol reagent. Goyer and Rhyne (1973) have indicated that lead ions tend to accumulate on cell surfaces, thereby possibly affecting surface receptors and cell-to-cell communication. A study by Koller and Brauner (1977) indicated that lead does alter C3b binding to its cell surface receptor.

12.8.8 Summary

Lead renders animals highly susceptible to endotoxins and infectious agents. Host susceptibility and the humoral immune system appear to be particularly sensitive. As postulated in recent studies, the macrophage may be the primary immune target cell of lead. Lead-induced immunosuppression occurs at low dosages that induce no evident toxicity and, therefore, may be detrimental to the health of animals and perhaps of humans. The data accumulated to date provide good evidence that lead affects immunity, but additional studies are necessary to elucidate the actual mechanism by which lead exerts its immunosuppressive action. Knowledge of lead effects of lead on the immune system of man is lacking and must be properly ascertained in order to determine permissible levels for human exposure. However, since this chemical affects immunity in laboratory animals and is immunosuppressive at very low dosages, its potential serious effects in man should be carefully considered.

12.9 EFFECTS OF LEAD ON OTHER ORGAN SYSTEMS

12.9.1 The Cardiovascular System

Since the best understood pathophysiologic mechanisms of hypertension in humans are those resulting from renal disease, the clinical evidence for a relationship between lead and hypertension is reviewed in Section 12.5.3.5 above. Under conditions of long-term lead exposure at high levels, arteriosclerotic changes have been demonstrated in the kidney. Dingwall-Fordyce and Lane (1963) reported a marked increase in the cerebrovascular mortality rate among heavily exposed lead workers as compared with the expected rate. These workers were exposed to lead during the first quarter of this century when working conditions were quite bad. There has been no similar increase in the mortality rate for men employed in recent times.

There are conflicting reports regarding whether lead can cause atherosclerosis in experimental animals. Scroczynski et al. (1967) observed increased serum lipoprotein and cholesterol levels and cholesterol deposits in the aortas of rats and rabbits receiving large doses of lead. On the other hand, Prerovská (1973), using similar doses of lead given over an even longer period of time, did not produce atherosclerotic lesions in rabbits.

Structural and functional changes have been noted in the myocardium of children with acute lead poisoning, but to date the extent of such studies has been limited. Cases have been described in adults and in children, always with clinical signs of poisoning. There is, of course, the possibility that the coexistence of lead poisoning and myocarditis is coincidental. In many cases in which encephalopathy is present, the electrocardiographic abnormalities disappeared with chelation therapy, suggesting that lead may have been the original etiological factor (Freeman, 1965; Myerson and Eisenhauer, 1963; Silver and Rodriguez-Torres, 1968). Silver and Rodriguez-Torres (1968) noted abnormal electrocardiograms in 21 of 30 children (70 percent) having symptoms of lead toxicity. After chelation therapy, the electrocardiograms remained abnormal in only four (13 percent) of the patients. Electron microscopy of the myocardium of lead-intoxicated rats (Asokan, 1974) and mice (Khan et al., 1977) have shown diffuse degenerative changes. Kopp and coworkers have demonstrated depression of contractility, isoproterenol responsiveness, and cardiac protein phosphorylation (Kopp et al., 1980a), as well as high energy phosphate levels (Kopp et al., 1980b) in hearts of lead-fed rats. Similarly, persistent increased susceptibility to norepinephrine-induced arrhythmias has been observed in rats fed lead during the first three weeks of life (Hejtmancik and Williams, 1977, 1978, 1979a,b; Williams et al., 1977a,b).

In a review of five fatal cases of lead poisoning in young children, degenerative changes in heart muscle were reported to be the proximate cause of death (Kline, 1960). It is not clear that such morphological changes are a specific response to lead intoxication. Kósmider and Petelnz (1962) examined 38 adults over 46 years of age with chronic lead poisoning. They

found that 66 percent had electrocardiographic changes, a rate that was four times the expected rate for that age group.

The cardiovascular effects of lead in conjunction with cadmium have been studied in rats following chronic low level exposure by Perry and coworkers (Perry and Erlanger, 1978; Kopp et al., 1980a,b). Perry and Erlanger (1978) exposed female weanling Long-Evans rats to cadmium, lead, or cadmium plus lead (as acetate salts) at concentrations of 0.1, 1.0, or 5.0 ppm in deionized drinking water for up to 18 months. These authors reported statistically significant increases in systolic blood pressure for both cadmium and lead in the range of 15-20 mm Hg. Concomitant exposure to both cadmium and lead usually doubled the pressor effects of either metal alone. A subsequent study (Kopp et al., 1980a) using weanling female Long-Evans rats exposed to 5.0 ppm cadmium, lead, or lead plus cadmium in deionized drinking water for 15 or 20 months showed similar pressor effects of these two metals alone or in combination on systolic blood pressure. Electrocardiograms performed on these rats demonstrated statistically significant prolongation of the mean PR interval. Bundle electrograms also showed statistically significant prolongations. Other parameters of cardiac function were not markedly affected. Phosphorus-31 nuclear magnetic resonance (NMR) studies conducted on perchloric acid extracts of liquid nitrogen-frozen cardiac tissue from these animals disclosed statistically significant reductions in adenosine triphosphate (ATP) levels and concomitant increases in adenosine diphosphate (ADP) levels. Cardiac glycerol 3-phosphoryl-choline (GPC) were also found to be significantly reduced using this technique, indicating a general reduction of tissue high-energy phosphates by lead or cadmium. Pulse-labeling studies using ^{32}P demonstrated decreased incorporation of this isotope into myosin light-chain (LC-2) in all lead or cadmium treatment groups relative to controls. The results of these studies indicate that prolonged low-dose exposure to lead (and/or cadmium) reduces tissue concentrations of high-energy phosphates in rat hearts and suggest that this effect may be responsible for decreased myosin LC-2 phosphorylation and subsequent reduced cardiac contractility. Other studies by these authors (Kopp et al., 1980b) were also conducted on isolated perfused hearts of weanling female Long-Evans rats exposed to cadmium, lead, or lead plus cadmium in deionized drinking water at concentrations of 50 ppm for 3-15 months. Incorporation of ^{32}P into cardiac proteins was studied following perfusion on inotropic perfusate containing isoproterenol at a concentration of 7×10^{-7} M. Data from these studies showed a statistically significant reduction in cardiac active tension in hearts from cadmium- or lead-treated rats. Phosphorus-32 incorporation was also found to be signficantly reduced in myosin LC-2 proteins. The authors suggested that the observed decrease in LC-2 phosphorylation could be involved in the observed decrease in cardiac active tension in lead- or cadmium-treated rats.

Makasev and Krivdina (1972) observed a two-phase change in the permeability of blood vessels (first increased, then decreased permeability) in rats, rabbits, and dogs that received a solution of lead acetate. A phase change in the content of catecholamines in the myocardium and in the blood vessels was observed in subacute lead poisoning in dogs (Mambeeva and Kobkova, 1969). This effect appears to be a link in the complex mechanism of the cardiovascular pathology of lead poisoning.

The susceptibility of the myocardium to toxic effects of lead was supported by in vitro studies in rat mitochondria by Parr and Harris (1976). These investigators found that the rate of Ca^{2+} removal by rat heart mitochondria is decreased by 1 nmol Pb/mg protein.

12.9.2 The Hepatic System

The effect of lead poisoning on liver function has not been extensively studied. In a study of 301 workers in a lead-smelting and refining facility, Cooper et al. (1973) found an increase in serum glutamic oxaloacetic transaminase (SGOT) activity in 11.5 percent of subjects with blood lead levels below 70 µg/dl, in 20 percent of those with blood lead levels of about 70 µg/dl, and in 50 percent of the workers with blood lead levels of about 100 µg/dl. The correlation ($r = 0.18$) between blood lead levels and SGOT was statistically significant. However, there must also have been exposure to other metals, e.g., cadmium, since there was a zinc plant in the smelter. In lead workers with moderate effects on the hematopoietic system and no obvious renal signs, SGOT was not increased compared with controls on repeated examinations (Hammond et al., 1980). In most studies on lead workers, tests for liver function are not included.

The liver is the major organ for the detoxification of drugs. In Section 12.3.1.3 it is mentioned that exposure to lead may cause altered drug detoxification rates as a result of interference with the formation of heme-containing cytochrome P-450, which is part of the hepatic mixed function oxidase system. This enzyme system is involved in the hepatic biotransformation of medicaments, hormones, and many environmental chemicals (Remmer et al., 1966). Whereas a decrease in drug-metabolizing activity clearly has been demonstrated in experimental animals given large doses of lead resulting in acute toxicity, the evidence for effects of that type in humans is less consistent. Alvares et al. (1975) studied the effect of lead exposure on drug metabolism in children. There were no differences between two normal children and eight children with biochemical signs of lead toxicity in their capacities to metabolize two test drugs, antipyrine and phenylbutazone. In two acutely poisoned children in whom blood levels of lead exceeded 60 µg/dl, antipyrine half-lives were significantly longer than normal, and therapy with EDTA led to biochemical remission of the disease and restoration of deranged drug metabolism toward normal. One of the "normal" children in this

study had a blood lead level of 40 µg/dl, but normal ALA-D and EP values. No data were given on the analytical methods used for indices of lead exposure. Furthermore, the age of the children varied from 1 to 7.5 years, which is significant because, as pointed out by the authors, drug detoxification is age-dependent.

Meredith et al. (1977) demonstrated enhanced hepatic metabolism of antipyrine in lead-exposed workers (PbB: 77-195 µg/dl) following chelation therapy. The significance of this evidence of restored hepatic mixed oxidase function is, however, unclear because the pretreatment antipyrine biologic half-life and clearance were not significantly different in lead-exposed and control subjects. Moreover, there were more heavy smokers among the lead-exposed workers than controls. Smoking increases the drug-metabolizing capacity and may thus counteract the effects of lead. Also, the effect of chelation on antipyrine metabolism in non-exposed control subjects was not determined.

Hepatic drug metabolism in eight adult patients showing marked effects of chronic lead intoxication on the erythropoietic system was studied by Alvares et al. (1976). The plasma elimination rate of antipyrine, which, as noted above, is a drug primarily metabolized by hepatic microsomal enzymes, was determined in eight subjects prior to and following chelation therapy. In seven of eight subjects, chelation therapy shortened the antipyrine half-lives, but the effect was minimal. The authors concluded that chronic lead exposure results in significant inhibition of the heme biosynthetic pathway without causing significant changes in enzymatic activities associated with hepatic cytochrome P-450.

A confounding factor in the above three studies may be that treatment with EDTA causes an increase in the glomerular filtration rate (GFR) if it has been reduced by lead (Section 12.5.3.3). This may cause a decrease in the half-times of drugs. There are, however, no data on the effect of chelating agents on GFR in children or adults with moderate signs of lead toxicity.

In 11 children with blood lead levels between 43 and 52 µg/dl, Saenger et al. (1981) found a decrease in 24-hour urinary 6-beta-hydroxycortisol excretion that correlated closely ($r = 0.85$, $p < 0.001$) with a standardized EDTA lead-mobilization test (1000 mg EDTA/m^2 body surface area). This glucocorticoid metabolite is produced by the same hepatic microsomal mixed function oxidase system that hydroxylates antipyrine. The authors suggest that the depression of 6-beta-hydroxylation of cortisol in the liver may provide a non-invasive method for assessing body lead stores in children (Saenger et al., 1981).

In a few animal studies special attention has been paid to morphological effects of lead on the liver. White (1977) gave eight beagle dogs oral doses of lead carbonate, 50-100 mg Pb/kg b.w., for 3-7 weeks. Lead concentrations were not measured in blood or tissues. In two dogs exposed from 5 weeks of age to 50 mg/kg, morphological changes were noted. Changes in

enzyme activities were noted in most exposed animals; for example, some dehydrogenases showed increased activity after short exposure and decreased activity after longer exposures, mainly in animals with weight losses. The small number of animals and the absence of data on lead concentrations makes it impossible to use these results for risk evaluations.

Hoffmann et al. (1974) noted moderate to marked morphological changes in baboon livers after a single intravenous injection of large doses of lead acetate (25 mg/kg b.w.). It can be concluded that effects on the liver may be expected to occur only at high exposure levels. If effects on more sensitive systems, viz., the nervous and hematopoietic systems, are prevented, no adverse effects should be noted in the liver.

12.9.3 The Endocrine System

The effects of lead on the endocrine or hormonal system are not well defined at the present time, but some evidence exists for such effects, at least at high levels of lead exposure. Lead is thought, for example, to decrease thyroid function in man and experimental animals. Porritt (1931) suggested that lead dissolved from lead pipes by soft water was the cause of hypothyroidism in individuals living in southwest England. Later, Kremer and Frank (1955) reported the simultaneous occurrence of myxedema and plumbism in a house painter. Monaenkova (1957) observed impaired concentration of ^{131}I by thyroid glands in 10 of 41 patients with industrial plumbism. Subsequently, Zel'tser (1962) showed that *in vivo* ^{131}I uptake and thyroxine synthesis by rat thyroid were decreased by lead when doses of 2 and 5 percent lead acetate solution were administered. Uptake of ^{131}I, sometimes decreased in men with lead poisoning, can be offset by treatment with thyroid-stimulating hormone (TSH) (Sandstead et al., 1969; Sandstead and Galloway, 1967). Lead may act to depress thyroid function by inhibiting thiol groups or by displacing iodine in a protein sulfonyl iodine carrier (Sandstead and Galloway, 1967), and the results suggest that excessive lead may act at both the pituitary and the thyroid gland itself to impair thyroid function. None of these effects on the thyroid system, however, have been demonstrated to occur in humans at blood lead levels below 30-40 µg/dl.

Sandstead et al. (1970a) studied the effects of lead intoxication on pituitary and adrenal function in man and found that it may produce clinically significant hypopituitarism in some. The effects of lead on adrenal function were less consistent, but some of the patients showed a decreased responsiveness to an inhibitor (metapyrone) of 11-beta-hydroxylation in the synthesis of cortisol. This suggests a possible impact of lead on pituitary-adrenal hormonal functions. That excessive oral ingestion of lead may in fact result in pathological changes in the pituitary-adrenal axis is also supported by other reports of lead-induced decreased metapyrone responsiveness, a depressed pituitary reserve, and decreased immunoreactive ACTH

(Murashov, 1966; Pines, 1965). These same events may also affect adrenal gland function as much as decreased urinary excretion of 17-hydroxy-corticosteroids was observed in these patients. Also, suppression of responsiveness to exogenous ACTH in the zona fasciculata of the adrenal cortex has been reported in lead-poisoned subjects (Makotchenko, 1965), and impairment of the zona glomerulosa of the adrenal cortex has also been suggested (Sandstead et al., 1970b). Once again, however, none of these effects on adrenal hormone function have been shown to occur at blood lead levels as low as 30-40 μg/dl.

Other studies provide evidence suggestive of lead exposure effects on endocrine systems controlling reproductive functions (see also Section 12.6). For example, evidence of abnormal luteinizing hormone (LH) secretory dynamics was found in secondary lead smelter workers (Braunstein et al., 1978). Reduced basal serum testosterone levels with normal basal LH levels but a diminished rise in LH following stimulation indicated suppression of hypothalamic-pituitary function. Testicular biopsies in two lead-poisoned workmen showed peritubular fibrosis suggesting direct toxic effects of lead in the testes as well as effects at the hypothalamic-pituitary level. Lancranjan et al. (1975) also reported lead-related interference with male reproductive functions. Moderately increased lead absorption (blood lead mean = 52.8 μg/dl) among a group of 150 workmen who had long-term exposure to lead in varying degrees was said to result in gonadal impairment. The effects on the testes were believed to be direct, however, in that tests for hypothalamic-pituitary influence were negative.

In regard to effects of lead on ovarian function in human females, Panova (1972) reported a study of 140 women working in a printing plant for 1 to 2 months, where ambient air lead levels were <7 $\mu g/m^3$. Using a classification of various age groups (20-25, 26-35, and 36-40 yr) and type of ovarian cycle (normal, anovular, and disturbed lutein phase), Panova claimed that statistically significant differences existed between the lead-exposed and control groups in the age range 20-25 years. It should be noted that the report does not show the age distribution, the level of significance, or the data on specificity of the method used for classification. Also, Zielhuis and Wibowo (1976), in a critical review of the above study, concluded that the design of the study and presentation of data are such that it is difficult to evaluate the author's conclusion that chronic exposure to low air lead levels leads to disturbed ovarian function. Moreover, no consideration was given to the dust levels of lead, an important factor in print shops. Unfortunately, little else besides the above report exists in the literature in regard to assessing lead effects on human ovarian function or other factors affecting human female fertility. Studies offering firm data on maternal variables, e.g., hormonal state, that are known to affect the ability of the pregnant woman to carry the fetus full-term are also lacking, although certain studies do indicate that at least high-level lead exposure induces stillbirths and abortions (see Section 12.6).

One animal study (Petrusz et al., 1979) indicates that orally administered lead can exert effects on pituitary and serum gonadotropins, which may represent one mechanism by which lead affects reproductive functions. The blood lead levels at which alterations in serum and pituitary follicle stimulating hormone were observed in neonatal rats, however, were well in excess of 100 µg/dl.

12.9.4 The Gastrointestinal System

Colic is usually a consistent early symptom of lead poisoning, warning of much more serious effects that are likely to occur with continued or more intense lead exposure. Although most commonly seen in industrial exposure cases, colic is also a lead-poisoning symptom present in infants and young children.

Beritic (1971) examined 64 men suffering from abdominal colic due to lead intoxication through occupational exposure. The diagnosis of lead colic was based on the occurrence of severe attacks of spasmodic abdominal pain accompanied by constipation, abnormally high coproporphyrinuria, excessive basophilic stippling, reticulocytosis, and some degree of anemia (all clinical signs of lead poisoning). Thirteen of the 64 patients had blood lead levels of 40-80 µg/dl upon admission. However, the report did not indicate how recently the patients' exposures had been terminated or provide other details of their exposure histories.

A more recent report by Dahlgren (1978) focused on the gastrointestinal symptoms of lead smelter workers whose blood lead levels were determined within two weeks of the termination of their work exposure. Of 34 workers with known lead exposure, 27 (79 percent) complained of abdominal pain, abnormal bowel movements, and nausea. Fifteen of the 27 had abdominal pain for more than 3 months after removal from the exposure to lead. The mean (and SD) blood lead concentration for this group of 15 was 70 (± 4) µg/dl. There was, however, no correlation between severity of symptoms and blood lead levels, as those experiencing stomach pain for less than 3 months averaged 68 (± 9) µg/dl and the remaining 7 workers, reporting no pain at all, averaged 76 (± 9) µg/dl.

Hänninen et al. (1979) assessed the incidence of gastrointestinal symptoms in 45 workers whose blood lead levels had been regularly monitored throughout their exposure and had never exceded 69 µg/dl. A significant association between gastrointestinal symptoms (particularly epigastric pain) and blood lead level was reported. This association was more pronounced in subjects whose maximal blood lead levels had reached 50-69 µg/dl, but was also noted in those whose blood lead levels were below 50 µg/dl.

Other occupational studies have also suggested a relationship between lead exposure and gastrointestinal symptoms (Lilis et al., 1977; Irwig et al., 1978; Fischbein et al., 1979, 1980). For demonstrating such a relationship, however, the most useful measure of internal

exposure has not necessarily been blood lead concentrations. Fischbein et al. (1980) surveyed a cross-section of New York City telephone cable splicers exposed to lead in the process of soldering cables. Of the 90 workers evaluated, 19 (21 percent) reported gastrointestinal symptoms related to lead colic. The difference between mean blood lead levels in those reporting GI symptoms and those not reporting such symptoms (30 vs. 27 μg/dl) was not statistically significant. However, mean zinc protoporphyrin concentrations (67 vs. 52 μg/dl) were significantly different ($p < 0.02$)

Although gastrointestinal symptoms of lead exposure are clinically evident in frank lead intoxication and may even be present when blood lead levels approach the 30-80 μg/dl range, there is currently insufficient information to establish a clear dose-effect relationship for the general population at ambient exposure levels.

12.10 CHAPTER SUMMARY

12.10.1 Introduction

Lead has diverse biological effects in humans and animals. Its effects are seen at the subcellular level of organellar structures and processes as well as at the overall level of general functioning that encompasses all systems of the body operating in a coordinated, interdependent fashion. The present chapter not only categorizes and describes the various biological effects of lead but also attempts to identify the exposure levels at which such effects occur and the mechanisms underlying them. The dose-response curve for the entire range of biological effects exerted by lead is rather broad, with certain biochemical changes occurring at relatively low levels of exposure and perturbations in other systems, such as the endocrine, becoming detectable only at relatively high exposure levels. In terms of relative vulnerability to deleterious effects of lead, the developing organism generally appears to be more sensitive than the mature individual. A more detailed and quantitative examination of overall exposure-effect relationships for lead is presented in Chapter 13.

12.10.2 Subcellular Effects of Lead

The biological basis of lead toxicity is its ability to bind to ligating groups in biomolecular substances crucial to various physiological functions, thereby interfering with these functions by, for example, competing with native essential metals for binding sites, inhibiting enzyme activity, and inhibiting or otherwise altering essential ion transport. These effects are modulated by: 1) the inherent stability of such binding sites for lead; 2) the compartmentalization kinetics governing lead distribution among body compartments, among tissues, and within cells; and 3) the differences in biochemical organization across cells and

tissues due to their specific functions. Given the complexities introduced by items 2 and 3, it is not surprising that no single unifying mechanism of lead toxicity across all tissues in humans and experimental animals has yet been demonstrated.

In so far as effects of lead on activity of various enzymes are concerned, many of the available studies concern in vitro behavior of relatively pure enzymes with marginal relevance to various effects in vivo. On the other hand, certain enzymes are basic to the effects of lead at the organ or organ system level, and discussion is best reserved for such effects in the summary sections below dealing with lead effects on particular organ systems. This section is mainly concerned with organellar effects of lead, expecially those which provide some rationale for lead toxicity at higher levels of biological organization. Particular emphasis is placed on the mitochondrion, because this organelle is not only affected by lead in numerous ways but has also provided the most data bearing on the subcellular effects of lead.

The critical target organelle for lead toxicity in a variety of cell and tissue types clearly is the mitochondrion, followed probably by cellular and intracellular membranes. The mitochondrial effects take the form of structural changes and marked disturbances in mitochondrial function within the cell, particularly in energy metabolism and ion transport. These effects in turn are associated with demonstrable accumulation of lead in mitochondria, both in vivo and in vitro. Structural changes include mitochondrial swelling in a variety of cell types as well as distortion and loss of cristae, which occur at relatively moderate lead levels. Similar changes have also been documented in lead workers across a range of exposures.

Uncoupled energy metabolism, inhibited cellular respiration using both succinate and nicotinamide adenine dinucleotide (NAD)-linked substrates, and altered kinetics of intracellular calcium have been demonstrated in vivo using mitochondria of brain and non-neural tissue. In some cases, the lead exposure level associated with such changes has been relatively low. Several studies document the relatively greater sensitivity of this organelle in young vs. adult animals in terms of mitochondrial respiration. The cerebellum appears to be particularly sensitive, providing a connection between mitochondrial impairment and lead encephalopathy. Impairment by lead of mitochondrial function in the developing brain has also been consistently associated with delayed brain development, as indexed by content of various cytochromes. In the rat pup, ongoing lead exposure from birth is required for this effect to be expressed, indicating that such exposure must occur before, and is inhibitory to, the burst of oxidative metabolism activity that occurs in the young rat at 10 to 21 days postnatally.

In vivo lead exposure of adult rats also markedly inhibits cerebral cortex intracellular calcium turnover in a cellular compartment that appears to be the mitochondrion. The effect was seen at a brain lead level of 0.4 ppm. These results are consistent with a separate study showing increased retention of calcium in the brain of lead-dosed guinea pigs. Numerous

reports have described the in vivo accumulation of lead in mitochondria of kidney, liver, spleen, and brain tissue, with one study showing that such uptake was slightly more than occurred in the cell nucleus. These data are not only consistent with deleterious effects of lead on mitochondria but are also supported by other investigations in vitro.

Significant decreases in mitochondrial respiration in vitro using both NAD-linked and succinate substrates have been observed for brain and non-neural tissue mitochondria in the presence of lead at micromolar levels. There appears to be substrate specificity in the inhibition of respiration across different tissues, which may be a factor in differential organ toxicity. Also, a number of enzymes involved in intermediary metabolism in isolated mitochondria have been observed to undergo significant inhibition of activity with lead.

Of particular interest regarding lead effects on isolated mitochondria are ion transport effects, especially in regard to calcium. Lead movement into brain and other tissue mitochondria involves active transport, as does calcium. Recent sophisticated kinetic analyses of desaturation curves for radiolabeled lead or calcium indicate that there is striking overlap in the cellular metabolism of calcium and lead. These studies not only establish the basis of lead's easy entry into cells and cell compartments, but also provide a basis for lead's impairment of intracellular ion transport, particularly in neural cell mitochondria, where the capacity for calcium transport is 20-fold higher than even in heart mitochondria.

Lead is also selectively taken up in isolated mitochondria in vitro, including the mitochondria of synaptosomes and brain capillaries. Given the diverse and extensive evidence of lead's impairment of mitochondrial structure and function as viewed from a subcellular level, it is not surprising that these derangements are logically held to be the basis of dysfunction of heme biosynthesis, erythropoiesis, and the central nervous system. Several key enzymes in the heme biosynthetic pathway are intramitochondrial, particularly ferrochelatase. Hence, it is to be expected that entry of lead into mitochondria will impair overall heme biosynthesis, and in fact this appears to be the case in the developing cerebellum. Furthermore, lead levels associated with entry of lead into mitochondria and expression of mitochondrial injury can be relatively moderate.

Lead exposure provokes a typical cellular reaction in human and other species that has been morphologically characterized as a lead-containing nuclear inclusion body. While it has been postulated that such inclusions constitute a cellular protection mechanism, such a mechanism is an imperfect one. Other organelles, e.g., the mitochondrion, also take up lead and sustain injury in the presence of nuclear inclusion formations.

In theory, the cell membrane is the first organelle to encounter lead and it is not surprising that cellular effects of lead can be ascribed to interactions at cellular and intracellular membranes in the form of distrubed ion transport. The inhibition of membrane

(Na^+,K^+)-ATPase of erythrocytes as a factor in lead-impaired erythropoiesis is noted elsewhere. Lead also appears to interfere with the normal processes of calcium transport across membranes of different tissues. In peripheral cholinergic synaptosomes, lead is associated with retarded release of acetylcholine owing to a blockade of calcium binding to the membrane, while calcium accumulation within nerve endings can be ascribed to inhibition of membrane (Na^+,K^+)-ATPase.

Lysosomes accumulate in renal proximal convoluted tubule cells of rats and rabbits given lead over a range of dosing. This also appears to occur in the kidneys of lead workers and seems to represent a disturbance in normal lysosomal function, with the accumulation of lysosomes being due to enhanced degradation of proteins because of the effects of lead elsewhere within the cell.

12.10.3. Effects of Lead on Heme Biosynthesis, Erythropoiesis, and Erythrocyte Physiology in Humans and Animals

The effects of lead on heme biosynthesis are well known both because of their prominence and the large number of studies of these effects in humans and experimental animals. The process of heme biosynthesis starts with glycine and succinyl-coenzyme A, proceeds through formation of protoporphyrin IX, and culminates with the insertion of divalent iron into the porphyrin ring, thus forming heme. In addition to being a constituent of hemoglobin, heme is the prosthetic group of numerous tissue hemoproteins having variable functions, such as myoglobin, the P-450 component of the mixed function oxygenase system, and the cytochromes of cellular energetics. Hence, disturbance of heme biosynthesis by lead poses the potential for multiple-organ toxicity.

The steps in the heme synthesis pathway that have been best studied in regard to lead effects involve three enzymes: (1) stimulation of mitochondrial delta-aminolevulinic acid synthetase (ALA-S), which mediates formation of delta-aminolevulinic acid (ALA); (2) direct inhibition of the cytosolic enzyme, delta-aminolevulinic acid dehydrase (ALA-D), which catalyzes formation of porphobilinogen from two units of ALA; and (3) inhibition of insertion of iron (II) into protoporphyrin IX to form heme, a process mediated by the enzyme ferrochelatase.

Increased ALA-S activity has been documented in lead workers as well as lead-exposed animals, although the converse, an actual decrease in enzyme activity, has also been observed in several experimental studies using different exposure methods. It would appear, then, that enzyme activity increase via feedback derepression or that activity inhibition may depend on the nature of the exposure. In an *in vitro* study using rat liver cells in culture, ALA-S activity could be stimulated at levels as low as 5.0 μM or 1.0 μg Pb/g preparation. In the same study, increased activity was seen to be due to biosynthesis of more enzyme. The threshold for lead stimulation of ALA-S activity in humans, based upon a study using leukocytes

from lead workers, appears to be about 40 µg Pb/dl. The generality of this threshold level to other tissues is dependent upon how well the sensitivity of leukocyte mitochondria mirrors that in other systems. It would appear that the relative impact of ALA-S activity stimulation on ALA accumulation at lower levels of lead exposure is considerably less than the effect of ALA-D activity inhibition: at 40 µg/dl blood lead, ALA-D activity is significantly depressed, while ALA-S activity only begins to be affected.

Erythrocyte ALA-D activity is very sensitive to lead inhibition, which is reversed by reactivation of the sulfhydryl group with agents such as dithiothreitol, zinc, or zinc plus glutathione. The zinc levels employed to achieve reactivation, however, are well above normal physiological levels. Although zinc appears to offset the inhibitory effects of lead observed in human erythrocytes in vitro and in animal studies, lead workers exposed to both zinc and lead do not show significant changes in the relationship of ALA-D activity to blood lead concentration when compared to workers exposed only to lead. By contrast, zinc deficiency in animals has been shown to significantly inhibit ALA-D activity, with concomitant accumulation of ALA in urine. Since zinc deficiency has also been associated with increased lead absorption in experimental studies, the possibility exists for a dual effect of such deficiency on ALA-D activity: (1) a direct effect on activity due to reduced zinc availability, as well as (2) the effect of increased lead absorption leading to further inhibition of such activity.

The activity of erythrocyte ALA-D appears to be inhibited at virtually all blood lead levels measured so far, and any threshold for this effect in either adults or children remains to be determined. A further measure of this enzyme's sensitivity to lead comes from a report noting that rat bone marrow suspensions show inhibition of ALA-D activity by lead at a level of 0.1 µg/g suspension. Inhibition of ALA-D activity in erythrocytes apparently reflects a similar effect in other tissues. Hepatic ALA-D activity was inversely correlated in lead workers with both the erythrocyte activity as well as blood lead. Of significance are the experimental animal data showing that (1) brain ALA-D activity is inhibited with lead exposure and (2) inhibition appears to occur to a greater extent in the brain of developing vs. adult animals. This presumably reflects greater retention of lead in developing animals. In the avian brain, cerebellar ALA-D activity is affected to a greater extent than that of the cerebrum and, relative to lead concentration, shows inhibition approaching that occurring in erythrocytes.

The inhibition of ALA-D activity by lead is reflected in increased levels of its substrate, ALA, in blood, urine, and tissues. In one investigation, the increase in urinary ALA was seen to be preceded by a rise in circulating levels of the metabolite. Blood ALA levels were elevated at all corresponding blood lead values down to the lowest value determined (18 µg/dl), while urinary ALA was seen to rise exponentially with blood ALA. Numerous independent

studies have documented that there is a direct correlation between blood lead and the logarithm of urinary ALA in adult humans and children, and that the threshold is commonly accepted as being 40 µg/dl. Several studies of lead workers also indicate that the correlation of urinary ALA with blood lead continues below this value. Furthermore, one report has demonstrated that the slope of the dose-effect curve in lead workers is dependent upon the level of exposure.

The health significance of lead-inhibited ALA-D activity and accumulation of ALA at low levels of exposure has been an issue of some controversy. One view is that the "reserve capacity" of ALA-D activity is such that only high accumulations of the enzyme's substrate, ALA, in accessible indicator media would result in significant inhibition of activity. One difficulty with this view is that it is not possible to quantify at lower levels of lead exposure the relationship of urinary ALA to levels in target tissues nor to relate the potential neurotoxicity of ALA at any level of build-up to levels in indicator media; i.e., the threshold for potential neurotoxicity of ALA in terms of blood lead may be different from the level associated with urinary accumulation.

Accumulation of protoporphyrin in the erythrocytes of individuals with lead intoxication has been recognized since the 1930s, but it has only recently been possible to quantitatively assess the nature of this effect via the development of specific, sensitive microanalysis methods. Accumulation of protoporphyrin IX in erythrocytes is the result of impaired placement of iron (II) in the porphyrin moiety to form heme, an intramitochondrial process mediated by the enzyme ferrochelatase. In lead exposure, the porphyrin acquires a zinc ion in lieu of native iron, thus forming zinc protoporphyrin (ZPP), and is tightly bound in available heme pockets for the life of the erythrocytes. This tight sequestration contrasts with the relatively mobile non-metal, or free, erythrocyte protoporphyrin (FEP) accumulated in the congenital disorder erythropoietic protoporphyria.

Elevation of erythrocyte ZPP has been extensively documented as being exponentially correlated with blood lead in children and adult lead workers and is presently considered one of the best indicators of undue lead exposure. Accumulation of ZPP only occurs in erythrocytes formed during lead's presence in erythroid tissue, resulting in a lag of at least several weeks before such build-up can be measured. It has been shown that the level of such accumulation in erythrocytes of newly-employed lead workers continues to increase when blood lead has already reached a plateau. This would influence the relative correlation of ZPP and blood lead in workers with a short exposure history. In individuals removed from occupational exposure, the ZPP level in blood declines much more slowly than blood lead, even years after removal from exposure or after a drop in blood lead. Hence, ZPP level would appear to be a more reliable indicator of continuing intoxication from lead resorbed from bone.

The measurable threshold for lead-induced ZPP accumulation is affected by the relative spread of blood lead and corresponding ZPP values measured. In young children (under four years old) the ZPP elevation typically associated with iron-deficiency anemia should be taken into account. In adults, several studies indicate that the threshold for ZPP elevation with respect to blood lead is approximately 25-30 µg/dl. In children 10-15 years old the threshold is about 16 µg/dl; in this age group, iron deficiency is not a factor. In one report, it was noted that children over four years old showed the same threshold, 15.5 µg/dl, as a second group under four years old, indicating that iron deficiency was not a factor in the study. Fifty percent of the children were found to have significantly elevated EP levels (2 standard deviations above reference mean EP) or a dose-response threshold level of 25 µg/dl.

Within the blood lead range considered "normal," i.e., below 30-40 µg/dl, any assessment of the ZPP-blood lead relationship is strongly influenced by the relative analytical proficiency for measurement of both blood lead and EP. The types of statistical treatments employed in analyzing the data are also important. In a recent detailed statistical study involving 2004 children, 1852 of whom had blood lead values below 30 µg/dl, segmental line and probit analysis techniques were employed to assess the dose-effect threshold and dose-response relationship. An average blood lead threshold for the effect using both statistical techniques yielded a value of 16.5 µg/dl for either the full group or those subjects with blood lead levels below 30 µg/dl. The effect of iron deficiency was tested for and removed. Of particular interest was the finding that the blood lead values corresponding to EP elevations more than 1 or 2 standard deviations above the reference mean in 50 percent of the children were 28.6 or 35.7 µg Pb/dl, respectively. Hence, fully half of the children were seen to have significant elevations of EP at blood lead levels around the currently accepted cut-off value for undue lead exposure, 30 µg/dl. From various reports, children and adult females appear to be more sensitive to the effects of lead on EP accumulation at any given blood lead level, with children being somewhat more sensitive than adult females.

Effects of lead on ZPP accumulation and reduced heme formation are not restricted to the erythropoietic system. Recent studies show that reduction of serum 1,25-dihydroxy vitamin D seen with even low level lead exposure is apparently the result of lead's inhibition of the activity of renal 1-hydroxylase, a cytochrome P-450 mediated enzyme. Cytochrome P-450, a heme-containing protein, is an integral part of the hepatic mixed function oxygenase system and is known to be affected in humans and animals by lead exposure, particularly acute intoxication. Reduced P-450 content has been found to be correlated with impaired activity of such detoxifying enzyme systems as aniline hydroxylase and aminopyrine demethylase.

Studies of organotypic chick dorsal root ganglion in culture show that the nervous system not only has heme biosynthetic capability but also such preparations elaborate porphyrinic material in the presence of lead. In the neonatal rat, chronic lead exposure resulting in

moderately elevated blood lead levels is associated with retarded growth in the hemoprotein cytochrome C and with disturbed electron transport in the developing rat cerebral cortex. These data parallel the effect of lead on ALA-D activity and ALA accumulation in neural tissue. When these effects are viewed in the toxicokinetic context of increased retention of lead in both developing animals and children, there is an obvious, serious potential for impaired heme-based metabolic function in the nervous system of lead-exposed children.

As can be seen from the above discussion, the health significance of ZPP accumulation rests with the fact that such build-up is evidence of impaired heme and hemoprotein formation in tissues, particularly the nervous system, arising from entry of lead into mitochondria. Such evidence for reduced heme synthesis is consistent with a diverse body of data documenting lead-associated effects on mitochondria, including impairment of ferrochelatase activity. As a mitochondrial enzyme, ferrochelatase activity may be inhibited either directly by lead or indirectly by impairment of iron transport to the enzyme.

The relative value of the lead-ZPP relationship in erythropoietic tissue as an index of this effect in other tissues hinges on the relative sensitivity of the erythropoietic system compared with other systems. For example, one study of rats exposed to low levels of lead over their lifetime demonstrated that protoporphyrin accumulation in renal tissue was already significant at levels of lead exposure where little change was seen in erythrocyte porphyrin levels. The issue of sensitivity is obviously distinct from the question of which system is most accessible to measurement of the effect.

Other steps in the heme biosynthesis pathway are also known to be affected by lead, although these have not been studied as much on a biochemical or molecular level. Levels of coproporphyrin are increased in urine, reflecting active lead intoxication. Lead also affects the activity of the enzyme uroporphyrinogen-I-synthetase, resulting in an accumulation of its substrate, porphobilinogen. The erythrocyte enzyme is much more sensitive to lead than the hepatic species and presumably accounts for much of the accumulated substrate.

Anemia is a manifestation of chronic lead intoxication, being characterized as mildly hypochromic and usually normocytic. It is associated with reticulocytosis, owing to shortened cell survival, and the variable presence of basophilic stippling. Its occurrence is due to both decreased production and increased rate of destruction of erythrocytes. In children under four years old, the anemia of iron deficiency is exacerbated by lead, and vice versa. Hemoglobin production is negatively correlated with blood lead levels in young children, where iron deficiency may be a confounding factor, as well as in lead workers. In one study, blood lead values that were usually below 80 µg/dl were inversely correlated with hemoglobin content. In these subjects, iron deficiency was found to be absent. The blood lead threshold for reduced hemoglobin content is about 50 µg/dl in adult lead workers and somewhat lower in children, around 40 µg/dl.

The mechanism of lead-associated anemia appears to be a combination of reduced hemoglobin production and shortened erythrocyte survival because of direct cell injury. Effects of lead on hemoglobin production involve disturbances of both heme and globin biosynthesis. The hemolytic component to lead-induced anemia appears to be due to increased cell fragility and increased osmotic resistance. In one study using rats, it was noted that the reduced cell deformability and consequent hemolysis associated with vitamin E deficiency is exacerbated by lead exposure. The molecular basis for increased cell destruction rests with inhibition of (Na^+, K^+)-ATPase and pyrimidine-5'-nucleotidase. Inhibition of the former enzyme leads to cell "shrinkage," and inhibition of the latter results in impaired pyrimidine nucleotide phosphorolysis and disturbance of the activity of the purine nucleotides necessary for cellular energetics.

Tetraethyl lead and tetramethyl lead, components of leaded gasoline, undergo transformation *in vivo* to the neurotoxic trialkyl metabolites as well as further conversion to inorganic lead. Hence, one might anticipate that exposure to such agents may show effects commonly associated with inorganic lead in terms of heme synthesis and erythropoiesis. Various surveys and case reports make it clear that leaded-gasoline sniffing is associated with chronic lead intoxication in children from socially deprived backgrounds in rural or remote areas. Notable in these subjects is evidence of impaired heme biosynthesis as indexed by significantly reduced ALA-D activity. In several case reports of frank lead toxicity from habitual sniffing of leaded gasoline, such effects as basophilic stippling in erythrocytes and significantly reduced hemoglobin have also been noted.

Lead-associated disturbances of heme biosynthesis as a possible factor underlying neurological effects of lead are of considerable interest because of (1) the recognized similarity between the classical signs of lead neurotoxicity and numerous neurological components of the congenital disorder known as acute intermittent porphyria, as well as (2) some unusual aspects of lead neurotoxicity. There are two possible points of connection between lead effects on both heme biosynthesis and the nervous system. Concerning the similarity of lead neurotoxicity to acute intermittent porphyria, there is the common feature of excessive systemic accumulation and excretion of ALA. Second, lead neurotoxicity reflects, to some degree, impaired synthesis of heme and hemoproteins involved in crucial cellular functions. Available information indicates that ALA levels are elevated in the brain of lead-exposed animals, arising via *in situ* inhibition of brain ALA-D activity or via transport to the brain after formation in other tissues. ALA is known to traverse the blood-brain barrier. Hence, ALA is accessible to, or formed within, the brain during lead exposure and may express its neurotoxic potential.

Based on various *in vitro* and *in vivo* data obtained in the context of neurochemical studies of lead neurotoxicity, it appears that ALA can readily affect GABAergic function, particularly inhibiting release of the neurotransmitter GABA from presynaptic receptors, where

ALA appears to be very potent even at low levels. In an in vitro study, agonist behavior by ALA was demonstrated at levels as low as 1.0 μM ALA. This in vitro observation supports results of a study using lead-exposed rats in which there was reported inhibition of both resting and K^+-stimulated preloaded ^{3}H-GABA. Further evidence for an effect of some agent other than lead acting directly is the observation that in vivo effects of lead on neurotransmitter function cannot be duplicated with in vitro preparations to which lead is added. Human data on lead-induced associations between disturbed heme synthesis and neurotoxicity, while limited, also suggest that ALA may function as a neurotoxicant.

The connection between impaired heme and hemoprotein synthesis in the brain of the neonatal rat was noted earlier. In these studies there was reduced cytochrome C production and impaired operation of the cytochrome C respiratory chain. Hence, one might expect that such impairment would be most prominent in areas of relatively greater cellularization, such as the hippocampus. As noted in Chapter 10, these are also regions where selective lead accumulation appears to occur.

12.10.4 Neurotoxic Effects of Lead

An assessment of the impact of lead on human and animal neurobehavioral function raises a number of issues. Among the key points addressed here are: (1) the internal exposure levels, as indexed by blood lead levels, at which various neurotoxic effects occur; (2) the persistence or reversibility of such effects; and (3) populations that appear to be most susceptible to neural damage. In addition, the question arises as to the utility of using animal studies to draw parallels to the human condition.

12.10.4.1 Internal Lead Levels at which Neurotoxic Effects Occur. Markedly elevated blood lead levels are associated with the most serious neurotoxic effects of lead exposure (including severe, irreversible brain damage as indexed by the occurrence of acute or chronic encephalopathic symptoms, or both) in both humans and animals. For most adult humans, such damage typically does not occur until blood lead levels exceed 120 μg/dl. Evidence does exist, however, for acute encephalopathy and death occurring in some human adults at blood lead levels below 120 μg/dl. In children, the effective blood lead level for producing encephalopathy or death is lower, starting at approximately 80-100 μg/dl. It should be emphasized that, once encephalopathy occurs, death is not an improbable outcome, regardless of the quality of medical treatment available at the time of acute crisis. In fact, certain diagnostic or treatment procedures themselves may exacerbate matters and push the outcome toward fatality if the nature and severity of the problem are not diagnosed or fully recognized. It is also crucial to note the rapidity with which acute encephalopathic symptoms can develop or death can occur in apparently asymptomatic individuals or in those apparently only

mildly affected by elevated lead body burdens. Rapid deterioration often occurs, with convulsions or coma suddenly appearing with progression to death within 48 hours. This strongly suggests that even in apparently asymptomatic individuals, rather severe neural damage probably exists at high blood lead levels even though it is not yet overtly manifested in obvious encephalopathic symptoms. This conclusion is further supported by numerous studies showing that overtly lead intoxicated children with high blood lead levels, but not observed to manifest acute encephalopathic symptoms, are permanently cognitively impaired, as are most children who survive acute episodes of frank lead encephalopathy.

Recent studies show that overt signs and symptoms of neurotoxicity (indicative of both CNS and peripheral nerve dysfunction) are detectable in some human adults at blood lead levels as low as 40-60 μg/dl, levels well below the 60 or 80 μg/dl criteria previously discussed as being "safe" for adult lead exposures. In addition, certain electrophysiological studies of peripheral nerve function in lead workers, indicate that slowing of nerve conduction velocities in some peripheral nerves are associated with blood lead levels as low as 30-50 μg/dl (with no clear threshold for the effect being evident). These results are indicative of neurological dysfunctions occurring at relatively low lead levels in non-overtly lead intoxicated adults.

Other evidence tends to confirm that neural dysfunctions exist in apparently asymptomatic children, at similar or even lower levels of blood lead. The body of studies on low-or moderate-level lead effects on neurobehavioral functions in non-overtly lead intoxicated children, as summarized in Table 12-1, presents an array of data pointing to that conclusion. Several well-controlled studies have found effects that are clearly statistically significant, whereas other have found nonsignificant but borderline effects. Even some studies reporting generally nonsignificant findings at times contain data confirming some statistically significant effects, which the authors attribute to various extraneous factors. It should also be noted that, given the apparent nonspecific nature of some of the behavioral or neural effects probable at low levels of lead exposure, one would not expect to find striking differences in every instance. The lowest observed blood lead levels associated with significant neurobehavioral deficits indicative of CNS dysfunction, both in apparently asymptomatic children and in developing rats and monkeys generally appear to be in the range of 30-50 μg/dl. However, other types of neurotoxic effects, e.g., altered EEG patterns, have been reported at lower levels, supporting a continuous dose-response relationship between lead and neurotoxicity. Such effects, when combined with adverse social factors (such as low parental IQ, low socioeconomic status, poor nutrition, and poor quality of the caregiving environment) can place children, especially those below the age of three years, at significant risk. However, it must be acknowledged that nutritional covariates, as well as demographic social factors, have

been poorly controlled in many of the human studies reviewed. Socioeconomic status also is a crude measure of parenting and family structure that requires further assessment as a possible contributor to observed results of neurobehavioral studies.

Timing, type, and duration of exposure are important factors in both animal and human studies. It is often uncertain whether observed blood lead levels represent the levels that were responsible for observed behavioral deficits or electrophysiological changes. Monitoring of lead exposures in human subjects in all cases has been highly intermittent or nonexistent during the period of life preceding neurobehavioral assessment. In most human studies, only one or two blood lead values are provided per subject. Tooth lead may be an important cumulative exposure index, but its modest, highly variable correlation to blood lead or FEP and to external exposure levels makes findings from various studies difficult to compare quantitatively. The complexity of the many important covariates and their interaction with dependent variable measures of modest validity, e.g., IQ tests, may also account for many of the discrepancies among the different studies.

12.10.4.2 Early Development and the Susceptibility to Neural Damage. On the question of early childhood vulnerability, the neurobehavioral data are consistent with morphological and biochemical studies of the susceptibility of the heme biosynthetic pathway to perturbation by lead. Various lines of evidence suggest that the order of susceptibility to lead's effects is: (1) young > adults and (2) female > male. Animal studies also have pointed to the perinatal period of ontogeny as a particularly critical time for a variety of reasons: (1) it is a period of rapid development of the nervous system; (2) it is a period where good nutrition is particularly critical; and (3) it is a period where the caregiver environment is vital to normal development. However, the precise boundaries of a critical period are not yet clear and may vary depending on the species and function or endpoint that is being assessed. Nevertheless, there is general agreement that human infants and toddlers below the age of three years are at special risk because of *in utero* exposure, increased opportunity for exposure because of normal mouthing behavior, and increased rates of lead absorption due to various factors, e.g., nutritional deficiences.

12.10.4.3 The Question of Irreversibility. Little research on humans is available on persistence of effects. Some work suggests that mild forms of peripheral neuropathy in lead workers may be reversible after termination of lead exposure, but little is known regarding the reversibility of lead effects on central nervous system function in humans. A recent two-year follow-up study of 28 children of battery factory workers found a continuing relationship between blood lead levels and altered slow wave voltage of cortical slow wave potentials indicative of persisting CNS effects of lead. Current population studies, however, will have to be supplemented by prospective longitudinal studies of the effects of lead on development in

order to address the issue of reversibility or persistence of lead neurotoxic effects in humans more satisfactorily.

Various animal studies provide evidence that alterations in neurobehavioral function may be long-lived, with such alterations being evident long after blood lead levels have returned to control levels. These persistent effects have been demonstrated in monkeys as well as rats under a variety of learning performance test paradigms. Such results are also consistent with morphological, electrophysiological, and biochemical studies on animals that suggest lasting changes in synaptogenesis, dendritic development, myelin and fiber tract formation, ionic mechanisms of neurotransmission, and energy metabolism.

12.10.4.4 Utility of Animal Studies in Drawing Parallels to the Human Condition. Animal models are used to shed light on questions where it is impractical or ethically unacceptable to use human subjects. This is particularly true in the case of exposure to environmental toxins such as lead. In the case of lead, it has been effective and convenient to expose developing animals via their mothers' milk or by gastric gavage, at least until weaning. In many studies, exposure was continued in the water or food for some time beyond weaning. This approach simulates at least two features commonly found in human exposure: oral intake and exposure during early development. The preweaning period in rats and mice is of particular relevance to in terms of parallels with the first two years or so of human brain development.

However, important questions exist concerning the comparability of animal models to humans. Given differences between humans, rats, and monkeys in heme chemistry, metabolism, and other aspects of physiology and anatomy, it is difficult to state what constitutes an equivalent internal exposure level (much less an equivalent external exposure level). For example, is a blood lead level of 30 µg/dl in a suckling rat equivalent to 30 µg/dl in a three-year-old child? Until an answer is available to this question, i.e., until the function describing the relationship of exposure indices in different species is available, the utility of animal models for deriving dose-response functions relevant to humans will be limited.

Questions also exist regarding the comparability of neurobehavioral effects in animals with human behavior and cognitive function. One difficulty in comparing behavioral endpoints such as locomotor activity is the lack of a consistent operational definition. In addition to the lack of standardized methodologies, behavior is notoriously difficult to "equate" or compare meaningfully across species because behavioral analogies do not demonstrate behavioral homologies. Thus, it is improper to assume, without knowing more about the responsible underlying neurological structures and processes, that a rat's performance on an operant conditioning schedule or a monkey's performance on a stimulus discrimination task corresponds to a child's performance on a cognitive function test. Still deficits in performance on such tasks are indicative of altered CNS function which is likely to parallel some type of altered human CNS function as well.

In terms of morphological findings, there are reports of hippocampal lesions in both lead-exposed rats and humans that are consistent with a number of behavioral findings suggesting an impaired ability to respond appropriately to altered contingencies for rewards. That is, subjects tend to persist in certain patterns of behavior even when changed conditions make the behavior inappropriate. Other morphological findings in animals, such as demyelination and glial cell decline, are comparable to human neuropathologic observations mainly at relatively high exposure levels.

Another neurobehavioral endpoint of interest in comparing human and animal neurotoxicity of lead is electrophysiological function. Alterations of electroencephalographic patterns and cortical slow wave voltage have been reported for lead-exposed children, and various electrophysiological alterations both in vivo (e.g., in rat visual evoked response) and in vitro (e.g., in frog miniature endplate potentials) have also been noted in laboratory animals. At this time, however, these lines of work have not converged sufficiently to allow for strong conclusions regarding the electrophysiological aspects of lead neurotoxicity.

Biochemical approaches to the experimental study of leads effects on the nervous system have generally been limited to laboratory animal subjects. Although their linkage to human neurobehavioral function is at this point somewhat speculative, such studies do provide insight to possible neurochemical intermediaries of lead neurotoxicity. No single neurotransmitter system has been shown to be particularly sensitive to the effects of lead exposure; lead-induced alterations have been demonstrated in various neurotransmitters, including dopamine, norepinephrine, serotonin, and gamma-aminobutyric acid. In addition, lead has been shown to have subcellular effects in the central nervous system at the level of mitochondrial function and protein synthesis.

Given the above-noted difficulties in formulating a comparative basis for internal exposure levels among different species, the primary value of many animal studies, particularly in vitro studies, may be in the information they can provide on basic mechanisms involved in lead neurotoxicity. A number of in vitro studies show that significant, potentially deleterious effects on nervous system function occur at in situ lead concentrations of 5 μM and possibly lower, suggesting that no threshold may exist for certain neurochemical effects of lead on a subcellular or molecular level. The relationship between blood lead levels and lead concentrations at such extra- or intracellular sites of action, however, remains to be determined. Despite the problems in generalizing from animals to humans, both the animal and the human studies show great internal consistency in that they support a continuous dose-response functional relationship between lead and neurotoxic biochemical, morphological, electrophysiological, and behavioral effects.

12.10.5 Effects of Lead on the Kidney

It has been known for more than a century that kidney disease can result from lead poisoning. Identifying the contributing causes and mechanisms of lead-induced nephropathy has been difficult, however, in part because of the complexities of human exposure to lead and other nephrotoxic agents.

Nevertheless, it is possible to estimate at least roughly lead exposure ranges associated with detectable renal dysfunction in both human adults and children. More specifically, numerous studies of occupationally exposed workers have provided evidence for lead-induced chronic nephropathy being associated with blood lead levels ranging from 40 to more than 100 μg/dl, and some are suggestive of renal effects possibly occurring even at levels as low as 30 μg/dl. Similarly, in children, the relatively sparse evidence available points to the manifestation of renal dysfunction, as indexed for example by generalized aminoaciduria, at blood lead levels across the range of 40 to more than 100 μg/dl. The current lack of evidence for renal dysfunction at lower blood lead levels in children may simply reflect the greater clinical concern with neurotoxic effects of lead intoxication in children. The persistence of lead-induced renal dysfunction in children also remains to be more fully investigated, although a few studies indicate that children diagnosed as being acutely lead poisoned experience lead nephropathy effects lasting throughout adulthood.

Parallel results from experimental animal studies reinforce the findings in humans and help illuminate the mechanisms underlying such effects. For example, a number of transient effects in human and animal renal function are consistent with experimental findings of reversible lesions such as nuclear inclusion bodies, cytomegaly, swollen mitochondria, and increased numbers of iron-containing lysosomes in proximal tubule cells. Irreversible lesions such as interstitial fibrosis are also well documented in both humans and animals following chronic exposure to high doses of lead. Functional renal changes observed in humans have also been confirmed in animal model systems with respect to increased excretion of amino acids and elevated serum urea nitrogen and uric acid concentrations. The inhibitory effects of lead exposure on renal blood flow and glomerular filtration rate are currently less clear in experimental model systems; further research is needed to clarify the effects of lead on these functional parameters in animals. Similarly, while lead-induced perturbation of the renin-angiotensin system has been demonstrated in experimental animal models, further research is needed to clarify the exact relationships among lead exposure (particularly chronic low-level exposure), alteration of the renin-angiotensin system, and hypertension in both humans and animals.

On the biochemical level, it appears that lead exposure produces changes at a number of sites. Inhibition of membrane marker enzymes, decreased mitochondrial respiratory function/

cellular energy production, inhibition of renal heme biosynthesis, and altered nucleic acid synthesis are the most marked changes to have been reported. The extent to which these mitochondrial alterations occur is probably mediated in part by the intracellular bioavailability of lead, which is determined by its binding to high affinity kidney cytosolic binding proteins and deposition within intranuclear inclusion bodies.

Recent studies in humans have indicated that the EDTA lead-mobilization test is the most reliable technique for detecting persons at risk for chronic nephropathy. Blood lead measurements are a less satisfactory indicator because they may not accurately reflect cumulative absorption some time after exposure to lead has terminated.

A number of major questions remain to be more definitively answered concerning the effect of lead on the kidney. Can a distinctive lead-induced renal lesion be identified either in functional or histologic terms? What biologic measurements are most reliable for the prediction of lead-induced nephropathy? What is the incidence of lead nephropathy in the general population as well as among specifically defined subgroups with varying exposure? What is the natural history of treated and untreated lead nephropathy? What is the mechanism of lead-induced hypertension and renal injury? What are the contributions of environmental and genetic factors to the appearance of renal injury due to lead? At what level of lead in blood can the kidneys be affected? Is there a threshold for renal effects of lead? The most difficult question to answer may well be to determine the contribution of low levels of lead exposure to renal disease of non-lead etiologies.

12.10.6 Effects of Lead on Reproduction and Development

Data from human and animal studies indicate that lead may exert gametotoxic, embryotoxic, and (according to some animal studies) teratogenic effects that may influence the survival and development of the fetus and newborn. Prenatal viability and development, it appears, may also be affected indirectly, contributing to concern for unborn children and, therefore, pregnant women or women of childbearing age being group at special risk for lead effects. Early studies of quite high dose lead exposure in pregnant women indicate toxic--but not teratogenic--effects on the conceptus. Effects on reproductive performance in women at lower exposure levels are not well documented. Unfortunately, currently available human data regarding lead effects on the fetus during development generally do not lend themselves to accurate estimation of lowest observed or no-effect levels. However, some studies have shown that fetal heme synthesis is affected at maternal and fetal blood lead levels as low as approximately 15 µg/dl, as indicated by urinary ALA levels and ALA-D activity. This observed effect level is consistant with lowest observed effect levels for indications of altered heme synthesis seen at later ages for preschool and older children.

There are currently no reliable data pointing to adverse effects in human offspring following paternal exposure to lead, but industrial exposure of men to lead at levels resulting in blood lead values of 40-50 µg/dl appear to have resulted in altered testicular function. Also, another study provided evidence of effects of prostatic and seminal vesicle functions at 40-50 µg/dl blood lead levels in lead workers.

The paucity of human exposure data force an examination of the animal studies for indications of threshold levels for effects of lead on the conceptus. It must be noted that the animal data are almost entirely derived from rodents. Based on these rodent data, it seems likely that fetotoxic effects have occurred in animals at chronic exposures to 600-1000 ppm lead in the diet. Subtle effects on fetal physiology and metabolism appear to have been observed in rats after chronic maternal exposure to 10 ppm lead in drinking water, while similar effects of inhaled lead have been seen at chronic levels of 10 mg/m^3. With acute exposure by gavage or by injection, the values are 10-16 mg/kg and 16-30 mg/kg, respectively. Since humans are most likely to be exposed to lead in their diet, air, or water, the data from other routes of exposure are of less value in estimating harmful exposures. Indeed, it seems likely that teratogenic effects occur only when the maternal dose is given by injection.

Although human and animal responses may be dissimilar, the animal evidence does document a variety of effects of lead exposure on reproduction and development. Measured or apparent changes in production of or response to reproductive hormones, toxic effects on the gonads, and toxic or teratogenic effects on the conceptus have all been reported. The animal data also suggest subtle effects on such parameters as metabolism and cell structure that should be monitored in human populations. Well designed human epidemiological studies involving large numbers of subjects are still needed. Such data could clarify the relationship of exposure levels and durations to blood lead values associated with significant effects, and are needed for estimation of no-effect levels.

Given that the most clear-cut data concerning the effects of lead on reproduction and development are derived from studies employing high lead doses in laboratory animals, there is still a need for more critical research to evaluate the possible subtle toxic effects of lead on the fetus, using biochemical, ultrastructural, or neurobehavioral endpoints. An exhaustive evaluation of lead-associated changes in offspring will require consideration of possible additional effects due to paternal lead burden. Neonatal lead intake via consumption of milk from lead-exposed mothers may also be a factor at times. Also, it must be recognized that lead effects on reproduction may be exacerbated by other environmental factors (e.g., dietary influences, maternal hyperthermia, hypoxia, and co-exposure to other toxins).

12.10.7. Genotoxic and Carcinogenic Effects of Lead

It is difficult to conclude what role lead may play in the induction of human neoplasia. Epidemiological studies of lead-exposed workers provide no definitive findings. However, statistically significant elevations in cancer of the respiratory tract and digestive system in workers exposed to lead and other agents warrant some concern. Since it is clear that lead acetate can produce renal tumors in some experimental animals, it seems reasonable to conclude that at least that particular lead compound should be regarded as a carcinogen and prudent to treat it as if it were also human carcinogen (as per IARC conclusions and recommendations). However, this statement is qualified by noting that lead has been seen to increase tumorogenesis rates in animals only at relatively high concentrations, and therefore does not seem to be an extremely potent carcinogen. In vitro studies further support the genotoxic and carcinogenic role of lead, but also indicate that lead is not extremely potent in these systems.

12.10.8. Effects of Lead on the Immune System

Lead renders animals highly susceptible to endotoxins and infectious agents. Host susceptibility and the humoral immune system appear to be particularly sensitive. As postulated in recent studies, the macrophage may be the primary immune target cell of lead. Lead-induced immunosuppression occurs at low lead exposures (blood lead levels in the 20-40 µg/dl range) that, although they induce no overt toxicity, may nevertheless be detrimental to health. Available data provide good evidence that lead affects immunity, but additional studies are necessary to elucidate the actual mechanisms by which lead exerts its immunosuppressive action. Knowledge of lead effects on the human immune system is lacking and must be ascertained in order to determine permissible levels for human exposure. However, in view of the fact that lead affects immunity in laboratory animals and is immunosuppressive at very low dosages, its potential for serious effects in humans should be carefully considered.

12.10.9 Effects of Lead on Other Organ Systems

The cardiovascular, hepatic, endocrine, and gastrointestional systems generally show signs of dysfunction mainly at relatively high lead exposure levels. Consequently, in most clinical and experimental studies attention has been primarily focused on more sensitive and vulnerable target organs, such as the hematopoietic and nervous systems. However, it should be noted that overt gastrointestinal symptoms associated with lead intoxication have been observed in some recent studies to occur in lead workers at blood lead levels as low as 40-60 µg/dl, suggesting that effects on the gastrointestinal and the other above organ systems may occur at relatively low exposure levels but remain to be demonstrated by future scientific investigations.

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APPENDIX 12-A
ASSESSMENT OF STUDIES REPORTING THE POTENTIAL ESSENTIALITY OF LEAD

Available information concerning the potential essentiality of lead is quite limited, due in part to the inherent difficulties surrounding such investigations. The presence of lead as a ubiquitous contaminant requires that studies of the effects of lead deficiency use synthetic or semi-synthetic diets prepared from components extremely low in lead or use chemical agents to reduce the level of background lead in the diet components. Such procedures, particularly the use of chelating agents to remove lead, can entail risk in terms of their potential effect on the nutritional integrity of the particular diet used.

Schwarz (1975) used synthetic diets prepared from low-lead constituents with or without lead supplementation to determine the effect of low lead on the growth rate of adult rats. It was reported that lead supplementation, usually over the range of 0.5 to 2.5 ppm lead, was associated with measurable enhancement in growth rate compared to low-lead animals. In a critique of the Schwarz results, Nielsen (1980) pointed out that all of the animals in the Schwarz study, both low-lead and supplementation groups, showed sub-optimal growth, which could be ascribed to riboflavin deficiency (Morgan and Schwarz, 1978); hence, the question remains as to what the effect of lead supplementation would be in animals not riboflavin-deficient and growing optimally. Nielsen (1980) has also questioned the statistical methods used in the Schwarz studies and pointed out that addition of lead to the diet was of no apparent benefit to deficient controls in subsequent studies. Problems associated with lead deprivation studies are exemplified by the inability of Schwarz to duplicate his growth rate data over time. He attributed this to the inadvertent use of a dietary component with an elevated lead content for diets of the low-lead animals.

In a series of recent reports, Reichlmayr-Lais and Kirchgessner have described results showing that rats maintained on a semi-synthetic diet low in lead (to levels of either 18 or 45 ppb) over several generations showed reduced growth rate (Reichlmayr-Lais and Kirchgessner, 1981a), disturbances in hematological indices, tissue iron and iron absorption (Reichlmayr-Lais and Kirchgessner, 1981b,c,d; Kirchgessner and Reichlmayr-Lais, 1981a,b), and changes in certain enzyme activities and metabolite levels (Reichlmayr-Lais and Kirchgessner, 1981e; Kirchgessner and Reichlmayr-Lais, 1982). Diets containing 18 ppb were associated with the most pronounced effects on iron metabolism and growth as well as on enzyme activities and metabolite levels. Animals maintained on a 45 ppb lead diet showed moderate changes in some hematological indices in the F_1-group. In these studies, controls were maintained on the same dietary matrix to which 1.0 ppm lead was added.

In the above reports, EDTA was used to remove lead (and other elements) from casein, and the chelating agent ammonium pyrrolidinodithiocarbamate (APDC) was employed to remove lead from the starch and cellulose components to achieve the final diet level of 18 ppb. For the 45 ppb diet experiment, only the starch and cellulose components were treated with APDC (Schnegg, 1975). Although the report of Reichlmayr-Lais and Kirchgessner (1981b) indicated that the cellulose and starch extraction treatment was done on all of the material, a communication in this regard (Kirchgessner, 1982) noted that only a portion of the starch and cellulose for the 45 ppb study was extracted with APDC. After chelant treatment, the components were washed with solvents to remove the complexed metals originally present. Washing was also assumed to remove the chelants.

Caution must be exercised in interpreting these studies as they currently stand, owing to the use of the chelating agents EDTA and/or APDC. Retention of free chelating agent(s) in the diets could potentially affect the bioavailability of certain metals. In the report of Davis et al. (1962), it was noted that diets containing soybean protein that had been extracted with EDTA to lower iron content, followed by supplementation with iron and copper, were associated with iron deficiency in chicks maintained on these diets when compared to chicks fed the same level of iron and copper in untreated diets. Clearly, EDTA treatment of the soybean protein affected iron bioavailability in this study. Subsequently, the authors (Davis et al., 1964) attempted to determine the presence of EDTA in the diets by simulating those used earlier. The crude methodology employed made accurate quantification difficult, but the amounts of EDTA measured ranged up to 67 µg/g diet. Other investigations through the years have documented that EDTA will affect iron absorption/retention and utilization in various species (e.g., Larsen et al., 1960; Brise and Hallberg, 1962; Saltman and Helbock, 1965; Günther, 1969; Cook and Monson, 1976).

In this connection, retention of EDTA by proteins appears to be a general problem, based on information available for casein (Hegenauer et al., 1979), transferrin (Price and Gibson, 1972), the enzyme alkaline phosphatase (Csopak and Szajn, 1973), photoprotein aequonin (Shimomura and Shimomura, 1982), and human fibrinogen (Nieuwenhuizen et al., 1981). Furthermore, complete removal of EDTA from these rather diverse proteins is reported to involve forcing conditions, and the washing procedure used by the authors of the studies in question gives no assurance of being adequate for chelant removal.

Available information also suggests that diets retaining free EDTA and/or APDC, even at quite low levels, may pose problems by affecting the bioavailability of the essential metal, nickel. The studies of Schnegg and Kirchgessner (see review of Kirchgessner and Schnegg, 1980) have shown that nickel deficiency in rats followed over several generations is associated with reduced growth rate, disturbed hematological indices, lowered tissue iron, reduced

iron absorption, and disturbances in enzyme activities and metabolite levels. According to Nielsen (1980), nickel plays a role in the intestinal absorption of trivalent iron. In the nickel deficiency studies of Schnegg and Kirchgessner, low-nickel diets contained 15 ppb nickel, while control groups were maintained on the same basal diet supplemented with 20 ppm nickel. In the lead deficiency studies under discussion, nickel was added back to the treated diets at a level of 1.0 ppm (Reichlmayr-Lais and Kirchgessner, 1981b; Kirchgessner and Reichlmayr-Lais, 1981b).

The interaction of nickel with the chelants EDTA and/or APDC in the context of bioavailability has been documented. Dithiocarbamates such as APDC are effective chelation therapy agents in protecting against nickel toxicity (see review of Sunderman, 1981), while the report of Solomons et al. (1982) described the significant effect of EDTA on nickel bioavailability in human subjects. In the latter study, human volunteers ingested a single dose of 5 mg of nickel, and the resulting effect on plasma nickel was monitored. When nickel was co-ingested with EDTA (40 mg of $Na_2EDTA \cdot H_2O$, a 1.3:1 ratio of EDTA to Ni), not only was the rise in plasma seen with just nickel abolished, but the plasma nickel level was reduced below the fasting background level.

It is not possible to draw a close comparison of the data of Schnegg and Kirchgessner for nickel deficiency with the potential effects of impaired nickel bioavailability in the lead deficiency studies since 1) the actual level of bioavailable nickel in the studies cannot be defined and 2) the age points for most of the effects seen in nickel deficiency are different from those in the lead studies. Interestingly, one can calculate that the decrements in body weight of animals of the F_1-generation in both groups of studies at various common time points, e.g., 20, 22, 30, 38 days, are virtually identical.

Any mechanism by which lead supplementation at 1.0 ppm in the lead deficiency studies would operate in a situtation of altered bioavailability of nickel or iron in the diets can only be inferred, given the absence of any further experiemental data which would more fully elucidate an essential vs. an artifactive role for lead.

In terms of any simple competitive binding mechanism involving lead, chelating agents, and nickel or iron, the presence of lead at a level of 1.0 ppm would be seen to most immediately affect nickel bound up with EDTA (as the common 1:1 complex) or APDC (as the common 1:2 complex). Nickel was added back to the diets at a level of 1.0 ppm. Since the binding constants for lead and nickel with EDTA are roughly comparable (Shapiro and Papa, 1959; Pribl, 1972), while complexes of lead with dithiocarbamates are vastly greater in stability than the corresponding nickel complexes (Sastri et al., 1969), lead at 1.0 ppm can displace up to its molar equivalent of nickel from complexation, which calculates to be 0.3 ppm nickel. This amount of liberated nickel, 0.3 ppm, appears to be nutritionally adequate, since the minimal

nutritional requirement is noted to be around 50 ppb (Kirchgessner and Schnegg, 1980; Nielson, 1980). The corresponding amounts of APDC and EDTA required to bind up 1.0 ppm nickel calculate to be 5.4 µg/g (1:2 complex, NiAPDC) and slightly under 5 µg/g (1:1 complex, Ni-EDTA). Hence, mere traces of free chelants could be a potential problem.

Similar direct competitive binding involving lead and iron cannot be invoked as likely, given the relative amounts of iron and lead in lead-supplemented diets, although lead forms more stable complexes than divalent iron with EDTA or APDC (Pribl, 1972; Sastri et al., 1969). A cyclic mechanism would have to be invoked whereby Pb-EDTA is formed by exchange of ligand from Fe-EDTA, is then dissociated in vivo, and the displacement process repeated.

Nickel supplementation at 20 ppm in the Schnegg and Kirchgessner studies, where a similar APDC procedure was used to purify starch and cellulose components, as well as in the study of Nielsen et al. (1979), where APDC at 10 ppm was employed to assess the role of nickel in iron metabolism, do not permit comparison with the studies in question because of the 20-fold disparity in the level of supplementation.

Given the above concerns, it would appear that: 1) further experiments, using methodology such as scintillography and labeled chelants, are necessary to conclusively determine that diet preparation in the Reichlmayr-Lais and Kirchgessner studies did not involve retention of free chelating agents, 2) determination of levels of nickel and lead in tissues, blood, and excreta would greatly help to elucidate the true role of lead, and 3) replication of the results in the authors' or another laboratory, preferably with minimal chelant treatment of components, should be done. It appears that the various reports describe basically single experiments over several generations, one at a diet level of 18 ppb lead, and one at 45 ppb lead.

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APPENDIX 12-B

SUMMARY OF PSYCHOMETRIC TESTS USED TO ASSESS COGNITIVE AND BEHAVIORAL DEVELOPMENT IN PEDIATRIC POPULATIONS

TABLE 128. TESTS COMMONLY USED IN A PSYCHO-EDUCATIONAL BATTERY FOR CHILDREN

	Age range	Norms	Scores	Advantages	Disadvantages
General Intelligence Tests					
Stanford-Binet (Form L-M)	2 yrs - Adult	1972	1. Deviation IQ: Mean = 100 SD = 16 2. Mental Age Equivalent	1. Good reliability & validity 2. Predicts school performance 3. Covers a wide age range	1. Tests mostly verbal skills especially after 6 yrs 2. Does not give a profile of skills
Wechsler Preschool & Primary Scales of Intelligence (WPPSI)	4 - 6½ yrs Best for 5-yr-olds	1967	1. Deviation IQ: Mean = 100 SD = 15 2. Scaled Scores for 10 sub tests: Mean = 10 SD = 3	1. Good reliability & validity 2. Predicts school performance 3. Gives a profile of verbal & non-verbal skills. 4. Useful in early identification of learning disability	1. Narrow age range 2. Mentally retarded children find this a disproportionate difficult test
Wechsler Intelligence Scale for Children-Revised (WISC-R)	6 - 16 yrs	1974	1. Deviation IQ: Mean = 100 SD = 15 2. Scaled Scores for 10 subtests: Mean = 10 SD = 3	1. Good reliability & validity 2. Predicts school performance 3. Gives a profile of verbal and non-verbal skills 4. Useful in identification of learning disability	1. Gives a lower IQ than Stanford-Binet for normal and bright children
McCarthy Scales of Children's Abilities (MSCA)	2½ - 8½ yrs Best for ages 4 - 6	1972	1. General Cognitive Index: Mean = 100 SD = 16 2. Scaled scores for 5 subtests: mean = 50 SD = 10 Age equivalents can be derived.	1. Good reliability & validity 2. Good predictor of school performance 3. Useful in identification of learning disabilities when given with a WISC-R or Stanford-Binet 4. Gives good information for educational programming	1. Children score much lower than on WISC-R or Stanford-Binet 2. Narrow age range
Bayley Scales of Mental Development	2 - 30 mos.	1969	1. Standard scores (M = 100 SD = 16) 2. Mental Development Psychomotor Index	1. Norms are excellent 2. Satisfactory reliability and validity 3. Best measure of infant development	1. Not a good predictor of later functioning in average as in below average children

TABLE 12B (continued)

	Age range	Norms	Scores	Advantages	Disadvantages
Slosson Intelligence Test	Infancy - 27 yrs	1963	1. Ratio IQ: is not related to general population	1. Good reliability & validity 2. Quick to administer. A good screening test	1. Many items taken from Stanford Binet 2. Responses require good language skills 3. Measures a narrow range of skills 4. A screening test: not to be used for classification or placement
Peabody Picture Vocabulary Test	2½ - 18 yrs	1959,rev.1981 White, Middle class sample	1. Verbal IQ 2. Age equivalent	1. Easily administered 2. Does not require language or motor skills	1. Fair reliability and validity 2. Tests only receptive vocabulary 3. Lower class children score lower 4. Mentally Retarded children score higher than on other tests 5. Not to be used for classification or placement.
Visual-Motor Tests					
Frostig Developmental Test of Visual Perception	3 - 8 yrs & older learning disabled (L.D.) children	1963 White, middle class sample	1. Perceptual Quotient: Median = 100 Quartile Deviation = 10 2. Perceptual Age Equivalent 3. Scaled Scores for 5 subtests	1. Good reliability for L.D. children	1. Fair reliability for normal children 2. Poor Validity 3. No known relationship to reading or learning 4. Remedial program based on test of questionable value 5. Not useful in identifying children at risk for L.D.
Bender-Gestalt	4 yrs - Adult	1964 Normal and Brain-injured Children	1. Age equivalent	1. Easily administered 2. Long history of research makes it a good research tool	1. Fair reliability 2. Poor predictive and validity 3. Responses influenced by fatigue & variations in administration 4. No known relationship to reading or subtle neurological dysfunction
Beery-Buktenica Developmental Test of Visual Motor Integration (VMI)	2 - 15 yrs	1967	1. Age equivalent	1. Easily administered 2. Good normative sample	1. Moderate reliability and validity 2. Correlates better with mental age than chronological age

TABLE 12B (continued)

	Age range	Norms	Scores	Advantages	Disadvantages
Educational Tests					
Wide Range Achievement Test (WRAT)	5 yrs - Adult	1976 Revised	1. Standard Score: mean = 100 SD = 15 2. Grade equivalent	1. Good reliability & validity Reading scores predict grade level 2. Tasks similar to actual work	1. Reading portion tests word recognition only 2. Responses require good organizational skills (could be an advantage)
Peabody Individual Achievement Test (PIAT)	5 - 18 yrs	1969	1. Standard Scores: Mean = 100 SD = 15 2. Grade equivalent 3. Age equivalent	1. Tests word recognition and 2. Breaks down skills into 5 areas	1. Moderate reliability. Low stability for Kindergarten 2. No data on predictive validity 3. A multiple choice test requiring child to recognize correct answer (could be an advantage). 4. Heavily loaded on verbal reasoning. 5. Factor structure changes with age.
Woodcock Reading Mastery Tests	Kgn - 12 grade	1971-72 adjusted for social class	1. Grade equivalent 2. Standard Score 3. Percentile Rank	1. Good reliability 2. Breakdown of reading skills useful diagnostically and in planning remediation 3. Easy to administer and score	1. No data on validity
Spache Diagnostic Reading Scales	1st - 8th grade	1972	1. Instructional level of reading (grade equivalent). 2. Independent level of reading. 3. Potential level of reading	1. Independent level score predicts gains following remediation 2. Good breakdown of reading skills	1. Fairly complex scoring 2. Moderate reliability 3. No good data on validity
Key Math Diagnostic Arithmetic Test	Pre-school - 6th grade	1971	1. Grade equivalent	1. Excellent breakdown of math skills 2. Easy to administer and score	1. Moderate reliability 2. No data on validity

TABLE 12B (continued)

	Age range	Norms	Scores	Advantages	Disadvantages
Tests of Adaptive Functioning					
Vineland Social Maturity Scale	Birth - 25 yrs	1983 Revised	1. Social Quotient (Ratio) 2. Social Age Equivalent	1. Easily administered 2. Good reliability for normal and MR chidren	1. Poor norms 2. No data on validity 3. Items are limited past preschool years 4. Scores decrease with age for MR children
AAMD Adaptive Behavior Scale	3 yrs - Adult	1974 Institutionalized Retardates; Public School Children (1982)	1. Percentile Ranks 2. Scaled scores	1. Discriminates between EMR and regular classes 2. Useful for class placement and monitoring progress	1. Moderate reliability for independent living skills scale. Poor reliability for maladaptive behaviour scale. 2. Lengthy administration 3. Items & scoring are not behaviorally objective
Progress Assessment Chart of Social Development (PAC)	Birth - Adult	1976	No Scores	1. Useful for training and assessing progress 2. Gives profile of skills	1. No data on reliability or validity
Developmental Profile	Birth - 12 yrs	1972	1. Age equivalents in 5 5 areas 2. IQ equivalency (IQE)	1. Good reliability and validity. Excellent study of construct validity reported in manual. 2. Gives a profile of skills	1. IQE underestimates IQ of above average children, overestimates IQ of below average children.
Conners Rating Scale	3 yrs - 17 yrs	1978	1. Age equivalents	1. Most widely used measure of attention deficit disorder 2. Four factors: conduct problems; hyperactivity; inattentive-passive; hyperactivity index	1. Parents' ratings don't predict as well as teachers' ratings 2. Works best middle class children
Werry-Weiss-Peters Hyperactivity Scale	1 yr - 9 yrs	1974, 1977	1. Age equivalents	1. Good measure of hyperactivity 2. Seven Factors	1. Limited age range 2. Standardized on middle class children

APPENDIX 12-C
WILL BE FORTHCOMING UNDER A SEPARATE COVER.

APPENDIX 12-D

ABSTRACT OF A REVIEW OF THREE STUDIES ON THE EFFECTS OF LEAD SMELTER EMISSIONS IN EL PASO, TEXAS

Presented by Warren R. Muir
Council on Environmental Quality
Washington, D.C.
At the International Conference on Heavy Metals in the Environment
Toronto, Ontario, Canada
October 1975

The committee reviewed two independent studies conducted in 1973 by Dr. Landrigan (CDC) and Dr. McNeil (ILZRO) to determine the effects of community lead exposures near the ASARCO smelter in El Paso, Texas. The CDC study used a random sample approach to group participating children, and in the ILZRO study match paired groups were selected on the basis of residence. In both studies the criteria for subclassification with regard to lead exposure were blood lead levels. Neuropsychological dysfunction was evaluated by several tests including WISC, WPPSI, and McCarthy scales. Statistical differences in test results could not be directly correlated to blood lead levels.

The opinion of the committee was that no firm conclusions could be drawn from the studies as to whether or not there are subclinical effects of lead on children in El Paso and that the reports and data made available have not clearly demonstrated any psychologic or neurologic effects in the children under study. It noted the absence of major chronic clinical effects, and concluded that these studies therefore do not bear upon the conclusions of other investigations under different conditions and those in which clinical effects have been confirmed. However, because of inherent problems of study design and the limitations in the tests used, this finding should not lead to a conclusion that low levels of lead have no effects on neuropsychological performance. Ellen Silbergeld, Ph.D., NIH, Eileen Higham, Ph.D., and Mr. Russell Jobaris, Johns Hopkins University, Department of Medical Psychology, served as special consultants.

The committee decided to limit its focus to a review of the three studies, and to attempt to account for and interpret the differences between the studies. Thus, aspects not related to differences were not emphasized.

The committee limited its consideration to the following materials: (1) reports of the three studies under consideration; (2) other materials provided by the authors of the studies; (3) background information and documents collected by Dr. Muir in El Paso. This presentation today consists of excerpts from a draft committee report.

D.1 HISTORY

El Paso is situated on the Mexican border in the western part of Texas. A lead smelter owned by American Smelting and Refining Company (ASARCO) has been located on the southwestern border of the city, on the Rio Grande River, since 1887. The area most conspicuously involved in the studies, Smeltertown, was a 2 x 6 block area located between the plant and the river. Smeltertown is no longer in existence, having been destroyed in December 1972. About 2 km south of Smeltertown is Old Fort Bliss, a considerably smaller community, whose inhabitants were considered in some, but not all, of the studies.

The ASARCO smelter produces lead, zinc, copper, and cadmium. Particulate matter is removed from airborne wastes in a series of baghouses; remaining emissions contain approximately 40 lb of lead per day.

The El Paso City County Health Department began an investigation of the ASARCO smelter in early 1970, in preparation for an air pollution suit filed by the city in April 1970. As part of this investigation, Dr.

Bertram Carnow was hired by the city as a consultant. At his suggestion, the city began to sample the blood lead levels of El Paso children to determine whether any had been over-exposed to lead. This included a large number of Smeltertown children. Based upon early results in 1971, Dr. Carnow visited El Paso, and saw a selected group of children with high blood lead levels. He interviewed the children, and reviewed their medical records. The information contained in the medical histories, and Dr. Carnow's interviews, constitute the observations reported by Dr. Carnow in the paper presented to the American Pollution Control Association (APCA). The clinical observations were in a paragraph of a paper otherwise devoted to a consideration of the effects of the smelter on the environment as a whole, and the extent of its emissions. This report contains no details on the age, exposures, individual signs and symptoms, or diagnostic criteria used in the ten cases reported. Our committee focused its attention, therefore, upon the two full-scale follow-up epidemiological studies conducted by Dr. Landrigan (CDC) and Dr. McNeil (ILZRO).

In 1973 ASARCO began a separate investigation of the population of Smeltertown, and asked Dr. James McNeil of the International Lead Zinc Research Organization (ILZRO) for his assistance in the examination and possible treatment of children with elevated blood levels greater than 60 mg/100 ml.

As a result of public concern over widespread lead poisoning throughout the city of El Paso, the mayor requested aid from the Federal Government. A separate protocol for a Center for Disease Control (CDC) study was submitted to and approved by the Public Health Board in 1973 with the understanding that the two studies would proceed independently, with those children in the ILZRO sponsored study being excluded from the CDC study.

In the summer of 1973, CDC and ILZRO proceeded independently to collect data for their respective studies. CDC's examinations were done in two weeks in June 1973, while McNeil's were carried out over the course of the summer with the aid of the El Paso public school system.

The CDC group supplied to the Committee data in detail, which were sufficient to allow the committee to conduct statistical tests and analyze characteristics of groups. For the ILZRO study, this committee requested data sufficient to carry out similar in-depth analyses. All of the requested data were supplied; however, they were not in such a form as to allow recalculation of most of the statistical findings of the study or to allow comparison with the CDC findings.

D.2 STUDY DESIGN

The environmental sampling that was performed was common for both of these studies. In the selection of study and control populations, the Landrigan CDC study used a classical approach of a random sample survey to determine the prevalence of abnormal blood lead values. The 13 census tracts most adjacent to the smelter were divided into three areas. The sampling frame was designed to obtain about 100 study subjects from each area for various age groups. Of 833 occupied residences, interviews were obtained from 758 study subjects in the 1-19 age group. The participating children were divided into a lead-absorption group (40-80 μg/100 ml) of 46 and a control group ($<$ 40 μg/100 ml) of 78. There is no detailed description as to how the children were chosen.

CDC used these same children as the basis for the later study of neuropsychological dysfunction. All but 3 children chosen for study came from the 1972 prevalence survey; 5 children with known preexisting defects such as with a history of symptoms compatible with acute lead poisoning or acute lead encephalopathy and those who had received chelation therapy were excluded.

While it is understood that a number of Smeltertown children with blood lead levels over 40 μg/100 ml were eventually involved in litigation, most of them took part in the studies. However, on the recommendation of the lawyers representing the children, at least one group of 18 did not participate in the ILZRO study. In the absence of identification by names of the individuals in the three studies, it has been impossible to evaluate the effects of non-participation.

The ILZRO study was very different; 138 children from Smeltertown agreed to participate in a study. Residence, not blood lead, was the selection criterion. Two control groups were chosen, and were reported to have been matched on age, sex, ethnic background, and income, with one set chosen from El Paso and another set for those 8 years of age or under from a rural area about 12 miles from the smelter. This classification had the effect of grouping together children who, under the CDC criteria, would have been in "lead" and "control" groups.

The criteria used for subclassification of children with regard to lead exposure were based in both studies on the blood lead level. Whereas the CDC study utilized blood lead values obtained at only two points in time, ILZRO, which was faced with the problem that many children had repeated blood lead measurements with marked variations over a period of 18 months (the levels being generally lower after exposure was discontinued), classified children on the basis of the average of the "two highest" recorded values.

This criterion results in a substantial increase in the number of children in the apparently higher blood lead category and a corresponding decrease in the number of those in the apparently lower blood lead level category.

Although it is understandable that this type of selection was used to avoid underestimating the problem of lead intoxication in the population examined, it ultimately resulted in muddling of the separation between groups (and possibly obscuring eventual differences). For example, the selection for analysis of children from the same geographical area, subclassified according to blood lead level, in the ILZRO study, may give the impression that the effects of lead itself are being studied in a homogeneous population. However, since exposure was geographically the same, other factors inherent to each individual child may be responsible for the difference in blood lead level observed.

An additional method of classification could have been the use of free erythrocytic protoporphyrin measurements (FEP) which have been shown to provide an indication of metabolic effects of lead absorption on metabolism, particularly useful in blood lead level ranges (40-60 μg/100 ml) where analytical and biological fluctuation may result in uncertain classification. (The ILZRO study included this test but did not include it as a basis for data analysis.) Absence of elevation of free erythrocytic protoporphyrin may indicate those instances where high blood lead levels were spurious.

The following psychometric tests were employed by the two studies:

1. Wechsler Intelligence Scale for Children, WISC (CDC, ILZRO)
2. McCarthy Scales of Children's Abilities (ILZRO)
3. Wechsler Preschool and Primary Scale of Intelligence, WPPSI (CDC)
4. Lincoln-Oseretsky Motor Development Scale (ILZRO)
5. California Test of Personality Adjustment (ILZRO)
6. Frosting Perceptual Quotient (ILZRO)
7. Bender Visual-Motor Gestalt Test (CDC, ILZRO)
8. Peabody
9. WRAT
10. Wepman
11. Draw-a-person

All of the tests selected by both studies were appropriate for the ages of the children to whom they were administered. Since the common ground for these studies is the WISC test, with the WPPSI used by CDC and the McCarthy Scales by ILZRO for the younger children in their studies, the Committee concentrated on these three tests and the results obtained for them.

D.3 RESULTS

The study by CDC reports results for 27 children given the WPPSI (12 with blood lead levels 40-80 μg/100 ml and 15 with blood lead levels less than 40 μg/100 ml) and for 97 children tested with the WISC (34 in the "lead group" and 63 in the "control group"). Statistical analyses were performed on grouped data with one-tailed tests. Significant differences between lead and control groups are reported in this study for the performance IQ's of the WICS and WPPSI. In subtest scores, significant differences were found in Coding on the WISC and Geometric Design on the WPPSI. When data from both tests are combined, a significant difference between lead and control groups on performance IQ is found. No differences were found between groups in verbal IQ's or full-scale IW's of the WISC or WPPSI.

The ILZRO study based on match pairing solely by residences reports no significant differences in scores on the WISC or McCarthy scales between groups with increased lead absorption and pair-matched controls. Statistical analysis was by means of two-way analysis of variance by age and blood lead levels.

The two studies base much of their conclusions upon psychometric and neurological testing of children from El Paso and Smeltertown. The reported significant differences and psychometric and neuromotor functions in the CDC study were clouded by potentially important methodological difficulties. These included

age differences between case and control groups, limited statistical treatment of the psychometric data collected, and, in the ILZRO study, the use of an average of the two highest blood lead levels to categorize lead exposure.

In addition, both the studies shared the following inherent problems:

1. Non-random exclusion of large groups of children
2. Uncertainties as to the selection of control groups
3. Reliance upon blood lead as the indicator of lead exposure and intoxication in analyses of data
4. Measurement of a limited aspect of psychological behavior
5. Lack of consideration of the potentially disruptive influences on test taking of the razing of Smeltertown, closing of its school, resettlement, litigation, and public controversy
6. Inability to rule out possible preexisting conditions

The Committee stressed the last issue, noting the likelihood that any behavioral or genetic factors that predispose an individual child to ingest or absorb more lead than another child equally exposed may itself be correlated to he result of psychometric testing. In other words an increased blood lead level may reflect, rather than cause, a preexisting difference in intelligence or behavior, an issue inherent in virtually all retrospective studies of the effects of low level blood lead.

The opinion of the committee was that no firm conclusions could be drawn from the studies as to whether or not there are subclinical effects of lead on children in El Paso and that the reports and data made available have not clearly demonstrated any psychologic or neurologic effects in the children under study. It noted the absence of major chronic clinical effects, and concluded that these studies therefore do not bear upon the conclusions of other investigations under different conditions and those in which clinical effects have been confirmed. However, because of inherent problems of study design and the limitations in the tests used, this finding should not lead to a conclusion that low levels of lead have no effects on neuropsychological performance.

13. EVALUATION OF HUMAN HEALTH RISKS ASSOCIATED WITH EXPOSURE TO LEAD AND ITS COMPOUNDS

13.1 INTRODUCTION

This chapter attempts to integrate, concisely, key information and conclusions discussed in preceding chapters into a coherent framework by which interpretation and judgments can be made concerning the risk to human health posed by present levels of lead contamination in the United States.

Towards this end, the chapter is organized into seven sections, each of which discusses one or more of the following major components of the overall health risk evaluation: (1) external and internal exposure aspects of lead; (2) lead metabolism, which determines the relationship of external lead exposure to associated health effects of lead; (3) qualitative and quantitative characterization of key health effects of lead; and (4) identification of population groups at special risk for health effects associated with lead exposure.

The various aspects of lead exposure discussed include: (1) an historical perspective on the input of lead into the environment as well as the nature and magnitude of current lead input; (2) the cycling of lead through the various environmental compartments; and (3) levels of lead in those media most relevant to lead exposure of various segments of the U.S. population. These various aspects of lead exposure are summarized in Section 13.2.

With respect to lead metabolism, some of the relevant issues addressed include: (1) the major quantitative characteristics of lead absorption, distribution, retention, and excretion in humans and how these differ between adults and children; (2) the toxicokinetic bases for external/internal lead exposure relationships with respect to both internal indicators and target tissue lead burdens; and (3) the relationships between internal and external indices of lead exposure, i.e., blood-lead levels in relation to lead concentrations in air, food, water, dust/soil. Section 13.3 summarizes the most salient features of lead metabolism, whereas Section 13.4 addresses experimental and epidemiological data concerning various blood lead-environmental media lead relationships.

In regard to various health effects of lead, the main emphasis here is on the identification of those effects most relevant to various segments of the general U.S. population and the placement of such effects in a dose-effect/dose-response framework. In regard to the latter, a crucial issue has to do with relative response of various segments of the population in terms of effect thresholds as indexed by some exposure indicator. Furthermore, it is of interest to assess the extent to which available information supports the notion of a continuum of effects as one proceeds across the spectrum of exposure levels. Finally, it is of interest to ascertain the availability of data on the relative number or percentage of members

(i.e., "responders") of specific population groups that can be expected to experience a particular effect at various lead exposure levels in order to permit delineation of dose-response curves for the relevant effects in different segments of the population. These matters are discussed in Sections 13.5 and 13.6.

Melding of information from the sections on lead exposure, metabolism, and biological effects permits the identification of population segments at special risk in terms of physiological and other host characteristics, as well as heightened vulnerability to a given effect; and these risk groups are discussed in Section 13.7. With demographic identification of individuals at risk, one may then draw upon population data from other sources to obtain a numerical picture of the magnitude of population groups at potential risk. This is also discussed in Section 13.7.

13.2 EXPOSURE ASPECTS

13.2.1 Sources of Lead Emission in the United States

The important issues to be raised concerning the sources of lead in the human environment are: What additional pathways to human consumption have been added in the course of civilization? What are the relative contributions of natural and anthropogenic lead? From the available data, what trends can be expected in the potential consumption of lead by humans? What is the impact of normal lead cycling processes on total human exposure? And finally, are there population segments particularly at risk due to a higher potential exposure?

Figure 13-1 is a composite of similar figures appearing in Chapters 7 and 11. This figure shows that four of the five sources of lead in the human environment are of anthropogenic origin. The only significant natural source is from the geochemical weathering of parent rock material as an input to soils. Of the four anthropogenic pathways, two are closely associated with atmospheric emissions and two (pigments and solder) are more directly related to the use of metallurgical compounds in products consumed by humans.

It is clear that natural sources contribute only a very small fraction to total lead in the biosphere. Levels of lead in the atmosphere, the main conduit for lead movement from sources into various environmental compartments are 10,000 to 20,000-fold higher in some urban areas than in the most remote regions of the earth. Chronological records assembled using reliable lead analysis techniques which show that atmospheric lead levels were at least 2,000-fold lower than at present before abrupt anthropological inputs accelerated with the industrial revolution and more recently, with the introduction of leaded gasoline. For actual comparison, estimates indicate a general background air lead level of 0.0005 μg Pb/m^3 versus

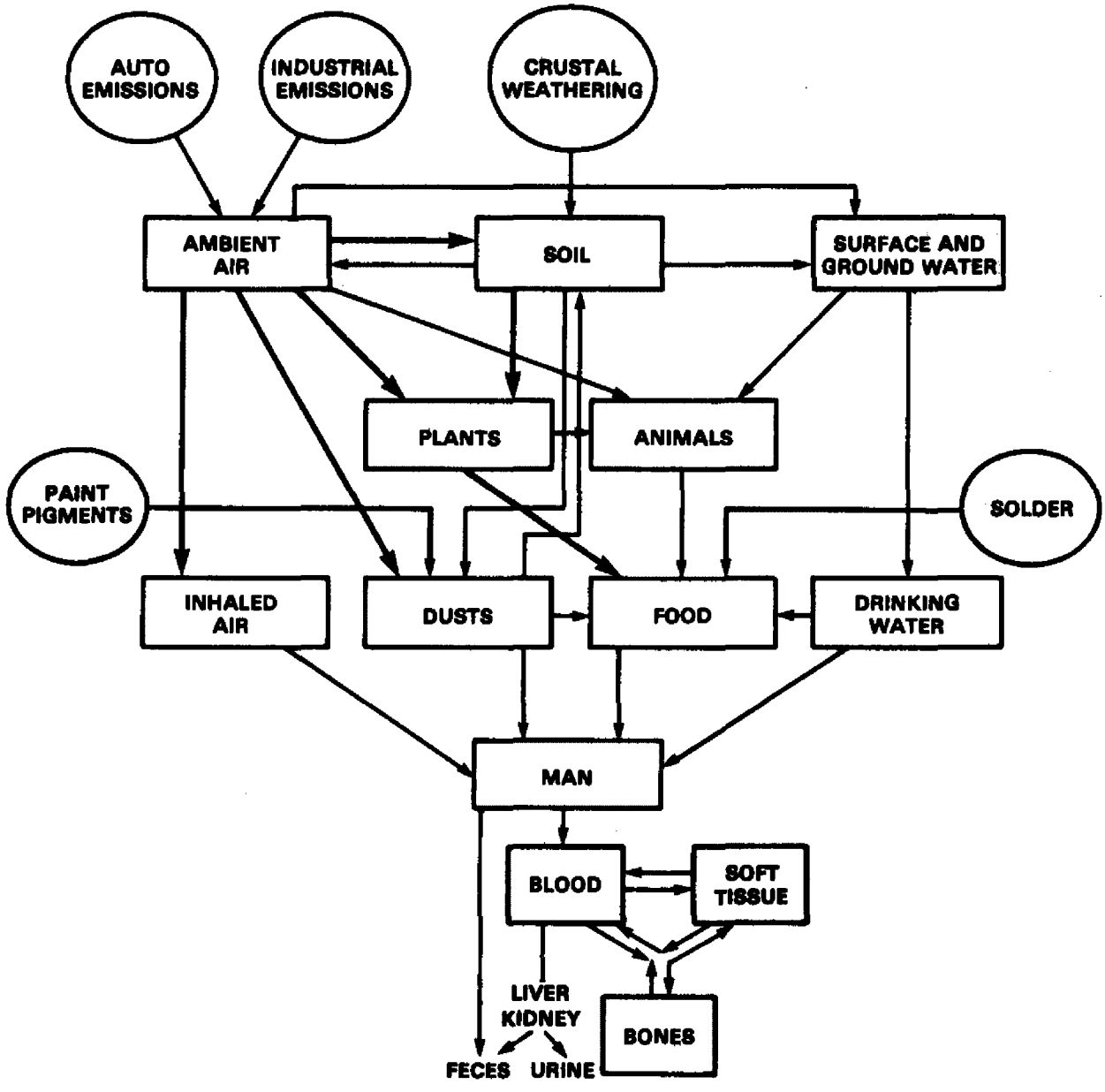

Figure 13-1. Pathways of lead from the environment to man.

urban air lead concentrations frequently approaching 1.0 μg Pb/m^3. A recent measurement of 0.000076 μg Pb/m^3 at the South Pole, using highly reliable lead analysis, suggests an anthropogenic enrichment factor of 13,000-fold compared to the same urban air level of 1.0 μg Pb/m^3.

Lead occupies an important niche in the U.S. economy, with consumption averaging 1.36 x 10^6 metric tons/year over the period 1971-1980. Of the various categories of lead consumption, those of pigments, gasoline additives, ammunition, foil, solder and steel products are widely dispersed and therefore unrecoverable. In the United States, about 41,000 tons are emitted to the atmosphere each year, including 35,000 tons as gasoline additives. Lead and its compounds enter the atmosphere at various points during mining, smelting, processing, use, recycling, or disposal. Leaded gasoline combustion in vehicles accounted for 86 percent of the total anthropogenic input into the atmosphere in the U.S. in 1981. Of the remaining 14 percent of total emissions from stationary sources, 7 percent was from the metallurgical industry, 2 percent was from waste oil combustion, and 2 percent from coal combustion. Atmospheric emissions have declined in recent years with the phase-down of lead in gasoline.

The fate of emitted particulate lead depends on particle size. It has been estimated that, of the 75 percent of combusted gasoline lead which immediately departs the vehicle in exhaust, 46 percent is in the form of particles <0.25 μm mass median equivalent diameter (MMED) and 54 percent has an average particle size of >10 μm. The sub-micron fraction is involved in long-range transport, whereas the larger particles settle mainly near the roadway.

13.2.2 Environmental Cycling of Lead

The atmosphere is the main conduit for movement of lead from emission sources to other environmental compartments. Removal of lead from the atmosphere occurs by both wet and dry deposition processes, each mechanism accounting for about one-half of the atmospheric lead removed. The fraction of lead emitted as alkyl lead vapor (1 to 6 percent) undergoes subsequent transformation to other, more stable compounds such as triethyl- or trimethyl lead, as a complex function of sunlight, temperature and ozone level.

Studies of the movement of lead emitted into the atmosphere indicate that air lead levels decrease logarithmically with distance away from the source: (1) away from emission sites, e.g., roadways and smelters; (2) within urban regions away from central business districts; (3) from urban to rural areas; and (4) from developed to remote areas.

By means of wet and dry deposition, atmospheric lead is transferred to terrestrial surfaces and bodies of water. Transfer to water occurs either directly from the atmosphere or through runoff from soil to surface waters. A sizeable fraction of water-borne lead becomes lodged in aquatic sediments. Percolation of water through soil does not transport much lead to ground water because most of the lead is retained at the soil surface.

The fate of lead particles on terrestrial surfaces depends upon such factors as the mechanism of deposition, the chemical form of the particulate lead, the chemical nature of the receiving soil, and the amount of vegetation cover. Lead deposited on soils is apparently immobilized by conversion to the carbonate, by binding to humic or fulvic acids, or by ion exchange on clays and hydrous oxides. In industrial, playground, and household environments, atmospheric particles accumulate as dusts with lead concentrations often greater than 1000 μg/g. It is important to distinguish these dusts from windblown soil dust, which typically has a lead concentration of 10 to 30 μg/g.

It has been estimated that soils adjacent to roadways have been enriched in lead content by as much as 10,000 μg Pb/g soil since 1930, while in urban areas and sites adjacent to smelters as much as 130,000 μg Pb/g has been measured in the upper 2.5 cm layer of soil.

Soil appears to be the major sink for emitted lead, with a residency half-time of decades; but soil as a reservoir for lead cannot be considered as an infinite sink, because lead will continue to pass into the grazing and detrital food chains and sustain elevated lead levels in them until equilibrium is reached. It was estimated in Chapters 7 and 8 that lead in soils not adjacent to major sources such as highways and smelters contain 3 to 5 μg/g of anthropogenic lead and that this lead has caused an increase of lead in soil moisture by a factor of 2 to 4. Thus, movement of lead from soils to other environmental compartments is at least twice the prehistoric rate and will continue to increase for the foreseeable future.

Lead enters the aquatic compartment by direct transfer from the atmosphere via wet and dry precipitation as well as indirectly from the terrestrial compartment via surface runoff. Water-borne lead, in turn, may be retained in some soluble fraction or may undergo sedimentation, depending on such factors as pH, temperature, suspended matter which may entrap lead, etc. Present levels of lead in natural waters represent a 50-fold enrichment over background content, from 0.02 to 1.0 μg Pb/l, due to anthropogenic activity. Surface waters receiving urban effluent represent a 2500-fold and higher enrichment (50 μg Pb/l and higher).

13.2.3 Levels of Lead in Various Media of Relevance to Human Exposure

Human populations in the United States are exposed to lead in air, food, water, and dust. In rural areas, Americans not occupationally exposed to lead consume 50 to 75 μg Pb/day. This level of exposure is referred to as the baseline exposure because it is unavoidable except by drastic change in lifestyle or by regulation of lead in foods or ambient air. There are several environmental circumstances that can increase human exposures above baseline levels. Most of these circumstances involve the accumulation of atmospheric dusts in the work and play environments. A few, such as pica and family home gardening, may involve consumption of lead from chips of exterior or interior house paint.

13.2.3.1 Ambient Air Lead Levels. Monitored ambient air lead concentration values in the U.S. are contained in two principal data bases: (1) EPA's National Air Sampling Network (NASN), recently renamed National Filter Analysis Network (NFAN); and (2) EPA's National Aerometric Data Bank, consistting of measurements by state and local agencies in conjunction with compliance monitoring for the current ambient air lead standard.

NASN data for 1982, the most current year in the annual surveys, indicate that most of the urban sites show reported annual averages below 0.7 μg Pb/m^3, while the majority of the non-urban locations have annual figures below 0.2 μg Pb/m^3. Over the interval 1976-1981, there has been a downward trend in these averages, mainly attributable to decreasing lead content of leaded gasoline and the increasing usage of lead-free gasoline. Furthermore, examination of quarterly averages over this interval shows a typical seasonal variation, characterized by maximum air lead values in winter and minimum values in summer.

With respect to the particle size distribution of ambient air lead, EPA studies using cascade impactors in six U.S. cities have indicated that 60 to 75 percent of such air lead was associated with sub-micron particles. This size distribution is significant in considering the distance particles may be transported and the deposition of particles in the pulmonary compartment of the respiratory tract. The relationship between airborne lead at the monitoring station and the lead inhaled by humans is complicated by such variables as vertical gradients, relative positions of the source, monitor, and the person, and the ratio of indoor to outdoor lead concentrations. To obtain an accurate picture of the amount of lead inhaled during the normal activities of an individual, personal monitors would probably be the most effective. But the information gained would be insignificant, considering that inhaled lead is only a small fraction of the total lead exposure, compared to the lead in food, beverages, and dust. The critical question with respect to airborne lead is how much lead becomes entrained in dust. In this respect, the existing monitoring network may provide an adequate estimate of the air concentration from which the rate of deposition can be determined. The percentage of ambient air lead which represents alkyl forms was noted in one study to range from 0.3 to 2.7 percent, rising up to about 10 percent at service stations.

13.2.3.2 Levels of Lead In Dust. The lead content of dusts can figure prominently in the total lead exposure picture for young children. Lead in aerosol particles deposited on rigid surfaces in urban areas (such as sidewalks, porches, steps, parking lots, etc.) does not undergo dilution compared to lead transferred by deposition onto soils. Dust can approach extremely high concentrations. Dust lead can accumulate in the interiors of dwellings as well as in the outside surroundings, particularly in urban areas.

Measurements of soil lead to a depth of 5 cm in areas of the U.S., using sites near roadways, were shown in one study to range from 150 to 500 μg Pb/g dry weight close to roadways

(i.e., within 8 meters). By contrast, lead in dusts deposited on or near heavily traveled traffic arteries show levels in major U.S. cities ranging up to 8000 μg Pb/g and higher. In residential areas, exterior dust lead levels are 1000 μg/g or less. Levels of lead in house dust can be significantly elevated. A study of house dust samples in Boston and New York City revealed levels of 1000 to 2000 μg Pb/g. Some soils adjacent to houses with exterior lead-based paints may have lead concentrations greater than 10,000 μg/g.

Thirty-four percent of the baseline consumption of lead by children comes from the consumption of 0.1 g of dust per day (Tables 13-1 and 13-2). Ninety percent of this dust lead is of atmospheric origin. Dust also accounts for more than ninety percent of the additive lead attributable to residences in an urban environment or near a smelter (Table 13-3).

13.2.3.3 Levels of Lead in Food. The route by which adults and older children in the baseline population of the U.S. receive the largest proportion of lead intake is through foods, with reported estimates of the dietary lead intake for Americans ranging from 60 to 75 μg/day. The added exposure from living in an urban environment is about 30 μg/day for adults and 100 μg/day for children, all of which can be attributed to atmospheric lead.

Atmospheric lead may be added to food crops in the field or pasture, during transportation to the market, during processing, and during kitchen preparation. Metallic lead, mainly solder, may be added during processing and packaging. Other sources of lead, as yet undetermined, increase the lead content of food between the field and dinner table. American children, adult females, and adult males consume 29, 33 and 46 μg Pb/day, respectively, in milk and nonbeverage foods. Of these amounts, 38 percent is of direct atmospheric origin, 36 percent is of metallic origin and 20 percent is of undetermined origin.

Processing of foods, particularly canning, can significantly add to their background lead content, although it appears that the impact of this is being lessened with the trend away from use of lead-soldered cans. The canning process can increase lead levels 8-to 10-fold higher than for the corresponding uncanned food items. Home food preparation can also be a source of additional lead in cases where food preparation surfaces are exposed to moderate amounts of high-lead household dust.

13.2.3.4 Lead Levels in Drinking Water. Lead in drinking water may result from contamination of the water source or from the use of lead materials in the water distribution system. Lead entry into drinking water from the latter is increased in water supplies which are plumbosolvent, i.e., with a pH below 6.5. Exposure of individuals occurs through direct ingestion of the water or via food preparation in such water.

The interim EPA drinking water standard for lead is 0.05 μg/g (50 μg/l) and several extensive surveys of public water supplies indicate that only a limited number of samples exceeded this standard on a nationwide basis. For example, a survey of interstate carrier water supplies conducted by EPA showed that only 0.3 percent exceeded the standard.

TABLE 13-1. SUMMARY OF BASELINE HUMAN EXPOSURES TO LEAD†

Source	Total Lead Consumed	Percent of Total Consumption	Soil		Direct Atmospheric Lead*	Lead from Solder or Other Metals	Lead of Undetermined Origin
			Natural Lead Consumed	Indirect Atmospheric Lead*			
Child 2-yr old							
Inhaled Air	0.5	0.8%	0.001	-	0.5	-	-
Food	28.7	46.7	0.9	0.9	10.9	10.3	17.6
Water & beverages	11.2	18.3	0.01	2.1	1.2	7.8	-
Dust	21.0	34.2	0.6	-	19.0	-	1.4
Total	61.4		1.5	3.0	31.6	18.1	19.0
Percent	100%		2.4%	4.9%	51.5%	29.5%	22.6%
Adult female							
Inhaled Air	1.0	1.8%	0.002	-	1.0	-	-
Food	33.2	58.7	1.0	1.0	12.6	11.9	21.6
Water & beverages	17.9	31.6	0.01	3.4	2.0	12.5	-
Dust	4.5	7.9	0.2	-	2.9	-	1.4
Total	56.6		1.2	4.4	18.5	24.4	23.0
Percent	100%		2.1%	7.8%	32.7%	43.1%	26.8%
Adult male							
Inahaled air	1.0	1.3%	0.002	-	1.0	-	-
Food	45.7	59.9	1.4	1.4	17.4	16.4	31.5
Water & beverages	25.1	32.9	0.1	4.7	2.8	17.5	-
Dust	4	5.9	0.2	-	2.9	-	1.4
Total	76.3		1.7	6.1	24.1	33.9	32.9
Percent	100%		2.2%	8.0%	31.6%	44.4%	27.1%

*Indirect atmospheric lead has been previously incorporated into soil, and will probably remain in the soil for decades or longer. Direct atmospheric lead has been deposited on the surfaces of vegetation and living areas or incorporated during food processing shortly before human consumption. It may be assumed that 85 percent of direct atmospheric lead derives from gasoline additives.

†units are in µg/day.

TABLE 13-2. RELATIVE BASELINE HUMAN LEAD EXPOSURES EXPRESSED PER KILOGRAM BODY WEIGHT*

	Total Lead Consumed	Total Lead Consumed Per Kg Body Wt µg/Kg·Day	Atmospheric Lead Per Kg Body Wt µg/Kg·Day
Child (2 yr old)	(µg/day)		
Inhaled air	0.5	0.05	0.05
Food	28.7	2.9	1.1
Water and beverages	11.2	1.1	0.12
Dust	21.0	2.1	1.9
Total	61.4	6.15	3.17
Adult female			
Inhaled air	1.0	0.02	0.02
Food	33.2	0.66	0.25
Water and beverages	17.9	0.34	0.04
Dust	4.5	0.09	0.06
Total	56.6	1.13	0.37
Adult male			
Inhaled air	1.0	0.014	0.014
Food	45.7	0.65	0.25
Water and beverages	25.1	0.36	0.04
Dust	4.5	0.064	0.04
Total	76.3	1.088	0.344

*Body weights: 2 year old child = 10/kg; adult female = 50 kg; adult male = 70 kg.

The major source of lead contamination of drinking water is the distribution system itself, particularly in older urban areas. Highest levels are encountered in "first-draw" samples, i.e., water sitting in the piping system for an extended period of time. In a large community water supply survey of 969 systems carried out in 1969-1970, it was found that the prevalence of samples exceeding 0.05 µg/g was greater where water was plumbo-solvent.

Most drinking water, and the beverages produced from drinking water, contain 0.008 to 0.02 µg Pb/g. The exceptions are canned juices and soda pop, which range from 0.033 to 0.052 µg/g. About 11 percent of the lead consumed in drinking water and beverages is of direct atmospheric origin, 70 percent comes from solder and other metals.

TABLE 13-3. SUMMARY OF POTENTIAL ADDITIVE EXPOSURES TO LEAD

	Total Lead Consumed (µg/day)	Atmospheric Lead Consumed (µg/day)	Other Lead Sources (µg/day)
Baseline exposure:			
Child (2 yr old)			
Inhaled air	0.5	0.5	-
Food, water & beverages	39.9	12.1	27.8
Dust	21.0	19.0	2.0
Total baseline	61.4	31.6	29.8
Additional exposure due to:			
urban atmospheres:[1]			
air inhalation	7	7	0
dust	72	71	1
family gardens[2]	800	200	600
interior lead paint[3]	85	-	85
residence near smelter:[4]			
air inhalation	60	60	-
dust	2250	2250	-
secondary occupational[5]	150	-	-
Baseline exposure:			
Adult Male			
Inhaled air	1.0	1.0	-
Food, water & beverages	70.8	20.2	50.6
Dust	4.5	2.9	1.6
Total baseline	76.3	24.1	52.2
Additional exposure due to:			
urban atmospheres:[1]			
air inhalation	14	14	-
dust	7	7	-
family gardens[2]	2000	500	1500
interior lead paint[3]	17	-	17
residence near smelter:[4]			
air inhalation	120	120	-
dust	250	250	-
occupational[6]	1100	1100	-
secondary occupational[5]	21	-	-
smoking	30	27	3
wine consumption	100	?	?

[1]includes lead from household and street dust (1000 µg/g) and inhaled air (.75 µg/m^3)

[2]assumes soil lead concentration of 2000 µg/g; all fresh leafy and root vegetables, sweet corn of Table 7-15 replaced by produce from garden. Also assumes 25% of soil lead is of atmospheric origin.

[3]assumes household dust rises from 300 to 2000 µg/g. Dust consumption remains the same as baseline. Does not include consumption of paint chips.

[4]assumes household and street dust increases to 25,000 µg/g, inhaled air increases to 6 µg/m^3.

[5]assumes household dust increases to 2400 µg/g.

[6]assumes 8 hr shift at 10 µg Pb/m^3 or 90% efficiency of respirators at 100 µg/ Pb/m^3. and occupational dusts at 100,000 µg/m^3.

13.2.3.5 Lead in Other Media. Flaking lead paint in deteriorated housing stock in urban areas of the Northeast and Midwest has long been recognized as a major source of lead exposure for young children residing in this housing stock, particularly for children with pica. Individuals who are cigarette smokers may inhale significant amounts of lead in tobacco smoke. One study has indicated that the smoking of 30 cigarettes daily results in lead intake equivalent to that of inhaling lead in ambient air at a level of 1.0 μg Pb/m^3.

13.2.3.6 Cumulative Human Lead Intake From Various Sources.

Table 13-1 shows the baseline of human lead exposures as described in detail in Chapter 7. These data show that atmospheric lead accounts for at least 30 percent of the baseline adult consumption and 50 percent of the daily consumption by a 2 yr old child. These percentages are conservative estimates because a part of the lead of undetermined origin may originate from atmospheric lead not yet accounted for.

From Table 13-2, it can be seen that young children have a dietary lead intake rate that is 5-fold greater than for adults, on a body weight basis. To these observations must be added that absorption rates for lead are higher in children than in adults by at least 3-fold. Overall, then, the rate of lead entry into the blood stream of children, on a body weight basis, is estimated to be twice that of adults from the respiratory tract and 6 and 9 times greater from the GI tract. Since children consume more dust than adults, the atmospheric fraction of the baseline exposure is ten-fold higher for children than for adults, on a body weight basis. These differences generally tend to place young children at greater risk, in terms of relative amounts of proportions of atmospheric lead absorbed per kg body weight, than adults under any given lead exposure situation.

13.3 LEAD METABOLISM: KEY ISSUES FOR HUMAN HEALTH RISK EVALUATION

From the detailed discussion of those various quantifiable characteristics of lead toxicokinetics in humans and animals presented in Chapter 10, several clear issues emerge as being important for full evaluation of the human health risk posed by lead:

1) Differences in systemic or internal lead exposure of groups within the general population in terms of such factors as age/development and nutritional status; and

2) The relationship of indices of internal lead exposures to both environmental levels of lead and tissues levels/effects.

Item 1 provides the basis for identifying segments within human populations at increased risk in terms of exposure criteria and is used along with additional information on relative sensitivity to lead health effects for identification of risk populations. The chief concern

with item 2 is the adequacy of current means for assessing internal lead exposure in terms of providing adequate margins of protection from lead exposures producing health effects of concern.

13.3.1 Differential Internal Lead Exposure Within Population Groups

Compared to adults, young children take in more lead through the gastrointestinal and respiratory tracts on a unit body weight basis, absorb a greater fraction of this lead intake, and also retain a greater proportion of the absorbed amount.

Unfortunately, such amplification of these basic toxicokinetic parameters in children vs. adults also occurs at the time when: (1) humans are developmentally more vulnerable to the effects of toxicants such as lead in terms of metabolic activity, and (2) the interactive relationships of lead with such factors as nutritive elements are such as to induce a negative course toward further exposure risk.

Typical of physiological differences in children vs. adults in terms of lead exposure implications is a more metabolically active skeletal system in children. In children, turnover rates of bone elements such as calcium and phosphorus are greater than in adults, with correspondingly greater mobility of bone-sequestered lead. This activity is a factor in the observation that the skeletal system of children is relatively less effective as a depository for lead than in adults.

Metabolic demand for nutrients, particularly calcium, iron, phosphorus, and the trace nutrients, is such that widespread deficiencies of these nutrients exist, particularly among poor children. The interactive relationships of these elements with lead are such that deficiency states both enhance lead absorption/retention and, as in the case of lead-induced reductions in 1,25-dihydroxyvitamin D, establish increasingly adverse interactive cycles.

Quite apart from the physiological differences which enhance internal lead exposure in children is the unique relationship of 2- to 3-year-olds to their exposure setting by way of normal mouthing behavior and the extreme manifestation of this behavior, pica. This behavior occurs in the same age group which studies have consistently identified as having a peak in blood lead. A number of investigations have addressed the quantification of this particular route of lead exposure, and it is by now clear that such exposure will dominate other routes when the child's surroundings, e.g., dust and soil, are significantly contaminated by lead.

Information provided in Chapter 10 also makes it clear that lead traverses the human placental barrier, with lead uptake by the fetus occurring throughout gestation. Such uptake of lead poses a potential threat to the fetus via an impact on the embryological developement of the central nervous and other systems. Hence, the only logical means of protecting the fetus from lead exposure is exposure control during pregnancy.

Within the general population, then, young children and pregnant women qualify as definable risk groups for lead exposure. Occupational exposure to lead, particularly among lead workers, logically defines these individuals as being in a high-risk category; work place contact is augmented by those same routes and levels of lead exposure affecting the rest of the adult population. From a biological point of view, lead workers do not differ from the general adult population with respect to the various toxicokinetic parameters and any differences in exposure control--occupational vs. non-occupational populations--as they exist are based on factors other than toxicokinetics.

13.3.2 Indices of Internal Lead Exposure and Their Relationship To External Lead Levels and Tissue Burdens/Effects

Several points are of importance in this area of lead toxicokinetics. They are: 1) the temporal characteristics of indices of lead exposure; 2) the relationship of the indicators to external lead levels; 3) the validity of indicators of exposure in reflecting target tissue burdens; 4) the interplay between these indicators and lead in body compartments; and 5) those various aspects of the issue with particular reference to children.

At this time, blood lead is widely held to be the most convenient, if imperfect, index of both lead exposure and relative risk for various adverse health effects. In terms of exposure, however, it is generally accepted that blood lead is a temporally variable measure which yields an index of relatively recent exposure because of the rather rapid clearance of absorbed lead from the blood. Such a measure, then, is of limited usefulness in cases where exposure is variable or intermittent over time, as is often the case with pediatric lead exposure.

Mineralizing tissue, specifically deciduous teeth, accumulate lead over time in proportion to the degree of lead exposure, and analysis of this material provides an assessment integrated over a greater time period and of more value in detecting early childhood exposure.

These two methods of assessing internal lead exposure have obvious shortcomings. A blood lead value will say little about any excessive lead intake at early periods, even though such remote exposure may have resulted in significant injury. On the other hand, whole tooth or dentine analysis is retrospective in nature and can only be done after the particularly vulnerable age in children under 4 to 5 years-- has passed. Such a measure, then provides little utility upon which to implement regulatory policy or clinical intervention.

The dilemmas posed by these existing methods may be able to be resolved by *in situ* analysis of teeth and bone lead, such that the intrinsic advantage of mineral tissue as a cumulative index is combined with measurement which is temporally concordant with on-going exposure. Work in several laboratories offers promise for such *in situ* analysis (See Chapters 9 and 10).

A second issue concerning internal indices of exposure and environmental lead is the relationship of changes in lead content of some medium with changes in blood content. Much of Chapter 11 was given over to description of the mathematical relationships of blood lead with lead in some external medium-- air, food, water, etc., without consideration of the biological underpinnings for these relationships.

Over a relatively broad range of lead exposure through some medium, the relationship of lead in the external medium to blood lead is curvilinear, such that relative change in blood lead per unit change in medium level generally becomes increasingly less as exposure increases. This behavior may reflect changes in tissue lead kinetics, reduced lead absorption, or increased excretion. Limited animal data would suggest that changes in excretion or absorption are not factors in this phenomenon. In any event, modest changes in blood levels with exposure at the higher end of this range are in no way to be taken as reflecting concomitantly modest changes in body or tissue lead uptake. Evidence continues to accumulate which suggests that an indicator such as blood lead is an imperfect measure of tissue lead burdens and of changes in such tissue levels in relation to changes in external exposure.

In Chapter 10, it was pointed out that blood lead is logarithmically related to chelatable lead (the latter being a more useful measure of the potentially toxic fraction of body lead), such that a unit change in blood lead is associated with an increasingly larger amount of chelatable lead. One consequence of this relationship is that moderately elevated blood lead values will tend to mask the "margin of safety" in terms of mobile body lead burdens. Such masking is apparent in one study of children where chelatable lead levels in children showing moderate elevations in blood lead overlapped those obtained in subjects showing frank plumbism, i.e. overt lead intoxication.

Related to the above is the question of the source of chelatable lead. It was noted in Chapter 10 that some sizable fraction of chelatable lead is derived from bone and this compels reappraisal of the notion that bone is an "inert sink" for otherwise toxic body lead.

The notion of bone lead as toxicologically inert never did accord with what was known from studies of bone physiology, i.e., that bone is a "living" organ, and the thrust of recent studies of chelatable lead as well as interrelationships of lead and bone metabolism is more to a view of bone lead as actually an insidious source of long-term systemic lead exposure rather than evidence of a protective mechanism permitting significant lead contact in industrialized populations.

The complex interrelationships of lead exposure, blood lead, and lead in body compartments is of particular interest in considering the disposition of lead in young children. Since children take in more lead on a weight basis, and absorb and retain more of this lead than the adult, one might expect that either tissue and blood levels would be significantly elevated or that the child's skeletal system would be more efficient in lead sequestration.

Blood lead levels in young children are either similar to adults (males) or somewhat higher (adult females). Limited autopsy data, furthermore, indicate that soft tissue levels in children are not markedly different from adults, whereas the skeletal system shows an approximate 2-fold increase in lead concentration from infancy to adolescence. Neglected in this observation is the fact that the skeletal system in children grows at an exponential rate, so that skeletal mass increases 40-fold during the interval in childhood when bone lead levels increase 2-fold, resulting in an actual increase of approximately 80-fold in total skeletal lead. If the skeletal growth factor is taken into account, along with growth in soft tissue and the expansion of vascular fluid volumes, the question of lead disposition in children is better understood.

Finally, limited animal data indicate that blood lead alterations with changes in lead exposure are poor indicators of such changes in target tissue. Specifically, it appears that abrupt reduction of lead exposure will be more rapidly reflected in blood lead than in such target tissues as the central nervous system, especially in the developing organism. This discordance may underlie the observation that severe lead neurotoxicity in children is associated with a rather broad range of blood lead values (see Section 12.4).

The above discussion of some of the problems with the use of blood lead in assessing target tissue burdens or the toxicologically active fraction of total body lead is really a summary of the inherent toxicokinetic problems with use of blood lead levels in defining margins of safety for avoiding internal exposure or undue risk of adverse effects.

If, for example, blood lead levels of 40-50 µg/dl in "asymptomatic" children are associated with chelatable lead burdens which overlap those encountered in frank pediatric plumbism, as documented in one series of lead-exposed children, then there is no margin of safety at these blood levels for severe effects which are not at all a matter of controversy. Were it both logistically feasible to do so on a large scale and were the use of chelants free of health risk to the subjects, serial provocative chelation testing would appear to be the better indicator of exposure and risk. Failing this, the only prudent alternative is the use of a large safety factor applied to blood lead which would translate to an "acceptable" chelatable burden. It is likely that this blood lead value would lie well below the currently accepted upper limit of 30 µg/dl, since the safety factor would have to be large enough to protect against frank plumbism as well as more subtle health effects seen with non-overt lead intoxication. This rationale from the standpoint of lead toxicokinetics is in accord also with the growing data base for dose-effect relationships of lead's effects on heme biosynthesis, erythropoiesis, and the nervous system in humans as detailed in Sections 12.3 and 12.4.

The future developement and routine use of <u>in situ</u> mineral tissue testing at time points concordant with on-going exposure and the comparison of such results with simultaneous blood

lead and chelatable lead measurement would be of significant value in further defining what level of blood lead is indeed an acceptable upper limit.

13.4 DEMOGRAPHIC CORRELATES OF HUMAN LEAD EXPOSURE AND RELATIONSHIPS BETWEEN EXTERNAL AND INTERNAL LEAD EXPOSURE INDICES

13.4.1 Demographic Correlates of Lead Exposure

Studies of ancient populations using bone and teeth show that levels of internal exposure of lead today are substantially elevated over past levels. Studies of current populations living in remote areas far from urbanized cultures show blood lead levels in the range of 1 to 5 µg/dl. In contrast to the blood lead levels found in remote populations, data from current U.S. populations have geometric means ranging from 10 to 20 µg/dl depending on age, race, sex and degree of urbanization. These increases of current exposure appear to be associated with industrialization and widespread commercial use of lead, for example gasoline combustion.

Age appears to be one of the single most important demographic covariate of blood lead levels. Blood lead levels in children up to six years are generally higher than those in non-occupationally exposed adults. Children aged two to three years tend to have the highest levels as shown in Figure 13-2. Blood lead levels in non-occupationally exposed adults may increase slightly with age due to skeletal lead accumulation.

Sex has a differential impact on blood lead levels depending on age. No significant differences exist between males and females less than seven years of age. Males above the age of seven generally have higher blood lead levels than females.

Race also plays a role, in that blacks have higher blood lead levels than either whites or Hispanics. Race has yet to be fully disentangled from exposure.

Blood lead levels also seem to increase with degree of urbanization. Data from NHANES II show that blood lead levels in the United States, averaged from 1976 to 1980, increase from a geometric mean of 11.9 µg/dl in rural populations to 12.8 µg/dl in urban populations less than one million, and increase again to 14.0 µg/dl in urban populations of one million or more.

Recent U.S. blood lead levels show a downward trend occurring consistently across race, age and geographic location. The downward pattern commenced in the early part of the 1970's and has continued into 1980. The downward trend has occurred from a shift in the entire distribution and not through a truncation in the high blood lead levels. This consistency suggests a general causative factor, and attempts have been made to identify the causative element. Reduction in lead emitted from the combustion of leaded gasoline is a prime candidate, but at present no causal relationship has been definitively established.

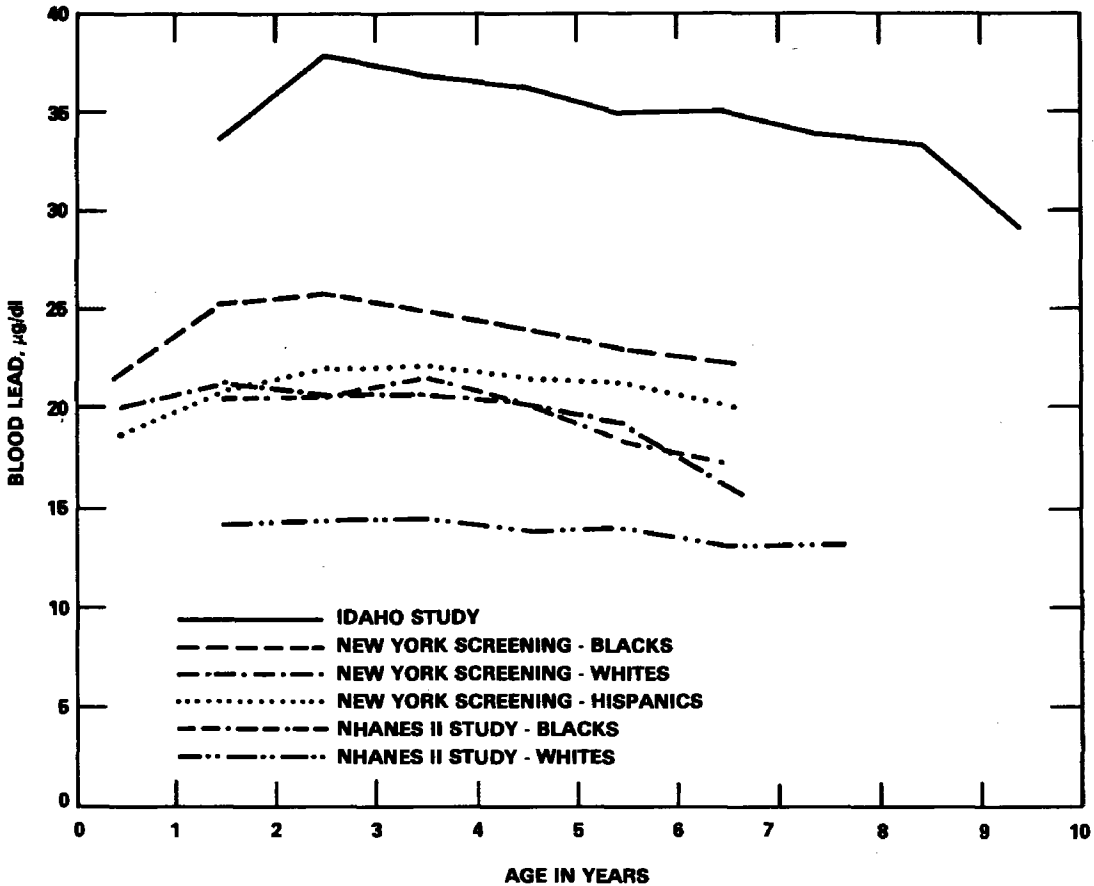

Figure 13 - 2. Geometric mean blood lead levels by race and age for younger children in the NHANES II study, and the Kellogg/Silver Valley and New York Childhood Screening Studies.

Blood lead levels, examined on a population basis, have similarly skewed distributions. Blood lead levels, from a population thought to be homogenous in terms of demographic and lead exposure characteristics, approximately follow a lognormal distribution. Geometric standard deviations, an estimation of dispersion, from four different studies discussed in Chapter 11, including analytic error, are about 1.4 for children and possibly somewhat smaller for adults. This allows an estimation of the upper tail of the blood lead distribution, which is the population segment in the United States at higher risk.

13.4.2 Relationships Between External and Internal Lead Exposure Indices

Because one main purpose of this chapter is to examine relationships of lead in air and lead in blood under ambient conditions, the results of studies most appropriate to this area have been emphasized. A summary of the most appropriate studies appears in Table 13-4. At air lead exposures of 3.2 $\mu g/m^3$ or less, there is no statistically significant difference between curvilinear and linear blood lead inhalation relationships. At air lead exposures at 10 $\mu g/m^3$ or more, either nonlinear or linear relationships can be fitted. Thus, a reasonably consistent picture emerges in which the blood lead air lead relationship by direct inhalation was approximately linear in the range of normal ambient exposures (0.1 - 2.0 $\mu g/m^3$) as discussed in Chapter 7. Differences among individuals in a given study, and among several studies are large, so that pooled estimates of the blood lead inhalation slope depend upon the the weight given to various studies. Several studies were selected for analysis, based upon factors described earlier. EPA analyses of experimental and clinical studies (Griffin et al., 1975; Rabinowitz et al., 1974, 1976, 1977; Kehoe 1961a,b,c; Gross 1981; Hammond et al., 1981) suggest that blood lead in adults increases by 1.64 ± 0.22 µg/dl from direct inhalation of each additional $\mu g/m^3$ of air lead. EPA analyses of population studies (Yankel et al., 1977; Roels et al., 1980; Angle and McIntire, 1979) suggest that, for children, the blood lead increase is 1.97 ± 0.39 µg/dl per $\mu g/m^3$ for air lead. EPA anaylsis of Azar's population study (Azar et al., 1975) yields a slope of 1.32 ± 0.38 for adult males.

These slope estimates are based on the assumption that an equilibrium level of blood lead is achieved within a few months after exposure begins. This is only approximately true, since lead stored in the skeleton may return to blood after some years. Chamberlain et al. (1978) suggest that long term inhalation slopes should be about 30 percent larger than these estimates. Inhalation slopes quoted here are associated with a half-life of blood lead in adults of about 30 days. O'Flaherty et al. (1982) suggest that the blood-lead half-life may increase slightly with duration of exposure, but this has not been confirmed (Kang et al., 1983).

One possible approach would be to regard all inhalation slope studies as equally informative and to calculate an average slope using reciprocal squared standard error estimates as

TABLE 13-4. SUMMARY OF BLOOD INHALATION SLOPES, (β)
$\mu g/dl$ per $\mu g/m^3$

POPULATION	STUDY	STUDY TYPE	N	(β) SLOPE $\mu g/dl$ per $\mu g/m^3$	MODEL SENSITIVITY OF SLOPE*
Children	Angle and McIntire, 1979 Omaha, NE	Population	1074	1.92	(1.40 - 4.40)[1,2,3]
	Roels et al. (1980) Belgium	Population	148	2.46	(1.55 - 2.46)[1,2]
	Yankel et al. (1977); Walter et al. (1980) Idaho	Population	879	1.52	(1.07 - 1.52)[1,2,3]
Adult Males	Azar et al. (1975). Five groups	Population	149	1.32	(1.08 - 2.39)[2,3]
	Griffin et al. (1975), NY prisoners	Experiment	43	1.75	(1.52 - 3.38)[4]
	Gross (1979)	Experiment	6	1.25	(1.25 - 1.55)[2]
	Rabinowitz et al. (1973,1976, 1977)	Experiment	5	2.14	(2.14 - 3.51)[5]

*Selected from among the most plausible statistically equivalent models. For nonlinear models, slope at 1.0 $\mu g/m^3$.

[1]Sensitive to choice of other correlated predictors such as dust and soil lead.

[2]Sensitive to linear vs. nonlinear at low air lead.

[3]Sensitive to age as a covariate.

[4]Sensitive to baseline changes in controls.

[5]Sensitive to assumed air lead exposure.

weights. This approach has been rejected for two reasons. First, the standard error estimates characterize only the internal precision of an estimated slope, not its representativeness (i.e., bias) or predictive validity. Secondly, experimental and clinical studies obtain more information from a single individual than do population studies. Thus, it may not be appropriate to combine the two types of studies.

Estimates of the inhalation slope for children are only available from population studies. The importance of dust ingestion as a non-inhalation pathway for children is established by many studies. A slope estimate has been derived for air lead inhalation based on those studies (Angle and McIntire 1979; Roels et al., 1980; Yankel et al., 1977) from which the air inhalation and dust ingestion contributions can both be estimated.

While direct inhalation of air lead is stressed, this is not the only air lead contribution that needs to be considered. Smelter studies allow partial assessment of the air lead contributions to soil, dust and finger lead. Conceptual models allow preliminary estimation of the propagation of lead through the total food chain as shown in Chapter 7. Useful mathematical models to quantify the propagation of lead through the food chain need to be developed. The direct inhalation relationship does provide useful information on changes in blood lead as responses to changes in air lead on a time scale of several months. The indirect pathways through dust and soil and through the food chain may thus delay the total blood lead response to changes in air lead, perhaps by one or more years. The Italian ILE study facilitates partial assessment of this delayed response from leaded gasoline as a source.

Dietary absorption of lead varies greatly from one person to another and depends on the physical and chemical form of the carrier, on nutritional status, and on whether lead is ingested with food or between meals. These distinctions are particularly important for consumption by children of leaded paint, dust and soil. Typical values of 10 percent absorption of ingested lead into blood have been assumed for adults and 25 to 50 percent for children.

It is difficult to determine accurate relationships between blood lead levels and lead levels in food or water. Dietary intake must be estimated by duplicate diets or fecal lead determinations. Water lead levels can be determined with some accuracy, but the varying amounts of water consumed by different individuals adds to the uncertainty of the estimated relationships.

Quantitative analyses relating blood lead levels and dietary lead exposures have been reported. Studies on infants provide estimates that are in close agreement. Only one individual study is available for adults (Sherlock et al. 1982); another estimate from a number of pooled studies is also available. These two estimates are in good agreement. Most of the subjects in the Sherlock et al. (1982) and United Kingdom Central Directorate on Environmental Pollution (1982) studies received quite high dietary lead levels (>300 µg/day). The fitted

cube root equations give high slopes at lower dietary lead levels. On the other hand, the linear slope of the United Kingdom Central Directorate on Environmental Pollution (1982) study is probably an underestimate of the slope at lower dietary lead levels. For these reasons, the Ryu et al. (1983) study is the most believable, although it only applies to infants. Estimates for adults should be taken from the experimental studies or calculated from assumed absorbtion and half-life values. Most of the dietary intake supplements were so high that many of the subjects had blood lead concentrations much in excess of 30 $\mu g/m^3$ for a considerable part of the experiment. Blood lead levels thus may not completely reflect lead exposure, due to the previously noted nonlinearity of blood lead response at high exposures. The slope estimates for adult dietary intake are about 0.02 µg/dl increase in blood lead per µg/day intake, but consideration of blood lead kinetics may increase this value to about 0.04. Such values are a bit lower than those estimated from the population studies extrapolated to typical dietary intakes about 0.05 µg/dl per µg/day. The value for infants is much larger.

The relation between blood lead and water lead is not clearly defined and is often described as nonlinear. Water lead intake varies greatly from one person to another. It has been assumed that children can absorb 25 to 50 percent of lead in water. Many authors chose to fit cube root models to their data, although polynomial and logarithmic models were also used. Unfortunately, the form of the model greatly influences the estimated contributions to blood lead levels from relatively low water lead concentration.

Although there is close agreement in the quantitative analyses of the relationship between blood lead level and dietary lead, there is a larger degree of variability in results of the various water lead studies. The relationship is curvilinear, but its exact form is yet to be determined. At typical levels for U.S. populations, the relationship appears linear. The only study that determines the relationship based on lower water lead values (<100 µg/l) is the Pocock et al. (1983) study. The data from this study, as well as the authors themselves, suggest that in this lower range of water lead levels, the relationship is linear. Furthermore, the estimated contributions to blood lead levels from this study are quite consistent with the polynomial models from other studies. For these reasons, the Pocock et al. (1983) slope of 0.06 is considered to represent the best estimate. The possibility still exists, however, that the higher estimates of the other studies may be correct in certain situations, especially at higher water lead levels (>100 µg/l).

Studies relating soil lead to blood lead levels are difficult to compare. The relationship obviously depends on depth of soil lead, age of the children, sampling method, cleanliness of the home, mouthing activities of the children, and possibly many other factors. Various soil sampling methods and sampling depths have been used over time, and as such they may not be directly comparable and may produce a dilution effect of the major lead concentration

contribution from dust which is located primarily in the top 2 cm of the soil. Increases in soil dust lead significantly increase blood lead in children. From several studies (Yankel et al., 1977; Angle and McIntire, 1979) EPA estimates an increase of 0.6 to 6.8 μg/dl in blood lead for each increase of 1000 μg/g in soil lead concentration. The values from the Stark et al. (1982) study of about 2, may represent a reasonable median estimate. The relationship of housedust lead to blood lead is difficult to obtain. Household dust also increases blood lead, children from the cleanest homes in the Silver Valley/Kellogg Study having 6 μg/dl less lead in blood, on average, than those from the households with the most dust.

A number of specific environmental sources of airborne lead have been evaluated for potential direct influence on blood lead levels. Combustion of leaded gasoline appears to be the largest contributor to airborne lead. Two studies used isotope ratios of lead to estimate the relative proportion of lead in the blood coming from airborne lead.

From the Manton study it can be estimated that between 7 to 41 percent of the blood lead in study subjects in Dallas resulted from airborne lead. Additionally, these data provide a means of estimating the indirect contribution of air lead to blood lead. By one estimate, only 10 to 20 percent of the total airborne contribution in Dallas is from direct inhalation.

From the ILE data of Facchetti and Geiss (1982), as shown in Table 13-5, the direct inhalation of air lead may account for 54 percent of the total adult blood lead uptake from leaded gasoline in a large urban center, but inhalation is a much less important pathway in

TABLE 13-5. ESTIMATED CONTRIBUTION OF LEADED GASOLINE TO BLOOD LEAD BY INHALATION AND NON-INHALATION PATHWAYS

Location	Air Lead Fraction From Gasoline[a]	Blood Lead Fraction From Gasoline[b]	Blood Lead From Gasoline In Air[c] (μg/dl)	Blood Lead Not Inhaled From Gasoline[d] (μg/dl)	Estimated Fraction Gas-Lead Inhalation[e]
Turin	0.873	0.237	2.79	2.37	0.54
<25 km	0.587	0.125	0.53	2.60	0.17
>25 km	0.587	0.110	0.28	3.22	0.08

[a]Fraction of air lead in Phase 2 attributable to lead in gasoline.

[b]Mean fraction of blood lead in Phase 2 attributable to lead in gasoline.

[c]Estimated blood lead from gas inhalation = β x (a) x (b), β = 1.6.

[d]Estimated blood lead from gas, non-inhalation = (f)-(e)

[e]Fraction of blood lead uptake from gasoline attributable to direct inhalation = (f)/(e)

Source: Facchetti and Geiss (1982), pp. 52-56.

suburban parts of the region (17 percent of the total gasoline lead contribution) and in the rural parts of the region (8 percent of the total gasoline lead contribution). EPA analyses of the preliminary results from the ILE study separated the inhalation and non-inhalation contributions of leaded gasoline to blood lead into the following three parts: (1) An increase of about 1.7 μg/dl in blood lead per μg/m^3 of air lead, attributable to direct inhalation of the combustion products of leaded gasoline; (2) a sex difference of about 2 μg/dl attributable to lower exposure of women to indirect (non-inhalation) pathways for gasoline lead; and (3) a non-inhalation background attributable to indirect gasoline lead pathways, such as ingestion of dust and food, increasing from about 2 μg/dl in Turin to 3 μg/dl in remote rural areas. The non-inhalation background represents only two to three years of environmental accumulation at the new experimental lead isotope ratio. It is not clear how to numerically extrapolate these estimates to U.S. subpopulations; but it is evident that even in rural and suburban parts of a metropolitan area, the indirect (non-inhalation) pathways for exposure to leaded gasoline make a significant contribution to blood lead. This can be seen in Table 13-5. It should also be noted that the blood lead isotope ratio responded fairly rapidly when the lead isotope ratio returned to its pre-experimental value, but it is not yet possible to estimate the long term change in blood lead attributable to persistent exposures to accumulated environmental lead.

Studies of data from blood lead screening programs suggest that the downward trend in blood lead levels noted earlier is due to the reduction in air lead levels, which has been attributed to the reduction of lead in gasoline.

Primary lead smelters, secondary lead smelters and battery plants emit lead directly into the air and ultimately increase soil and dust lead concentrations in their vicinity. Adults, and especially children, have been shown to exhibit elevated blood lead levels when living close to these sources. Blood lead levels in these residents have been shown to be related to air, as well as to soil or dust exposures.

13.4.3 Proportional Contributions of Lead in Various Media to Blood Lead in Human Populations

The various mathematical descriptions of the relationship of blood lead to lead in individual media--air, food, water, dust, soil--were discussed in some detail in Chapter 11 and concisely in the preceding section (13.4.2) of this chapter. Using values for lead intake/content of these media which appear to represent the current exposure picture for human populations in the U.S., these relationships are further employed in this section to estimate proportional inputs to total blood lead levels in U.S. populations. Such an exercise is of help in providing an overall perspective on which routes of exposure are of most significance in terms of contributions to blood lead levels seen in U.S. populations.

Table 13-6 tabulates the relative direct contributions (in percentages) of air lead to blood lead at different air-lead levels for calculated typical background levels of lead from food and water in adults. The blood lead contributions from diet are estimated using the slope 0.02 µg/dl increase in blood lead µg/day intake as discussed in Section 11.4.2.4.

TABLE 13-6. DIRECT CONTRIBUTIONS OF AIR LEAD TO BLOOD LEAD (PbB) IN ADULTS AT FIXED INPUTS OF WATER AND FOOD LEAD

Air Lead ($\mu g/m^3$)	PbB (Air)[a]	PbB (Food)[b]	PbB (Water)[c]	% PbB From Air
0.1	0.2	2.0	0.6	7.1
1.0	2.0	2.0	0.6	43.4
1.5	3.0	2.0	0.6	53.5

[a] $\frac{\Delta \text{ PbB}}{\Delta \text{ Pb Air}} = 2.0$ for 3.2 $\mu g/m^3$ or less.

[b] Assuming 100 µg/day lead from diet and slope 0.02 as discussed in Section 11.4.2.4.

[c] Assuming 10 µg/ℓ water, Pocock et al. (1983).

In Table 13-7 are listed the direct contributions of air lead to blood lead at varying air lead levels for children given calculated typical background levels of blood lead for food and water. Diet contribution is based on the work of Ryu et al. (1983). Table 13-8 shows the relative contributions of dust/soil to blood lead at varying dust/soil levels for children given calculated background levels of blood lead from air, food, and water. Assuming that virtually all soil/dust lead is due to atmospheric fallout of lead particles, the percentage contribution of air directly and indirectly to blood lead becomes significantly greater than when considering just the direct impact of inhaling lead in the ambient air.

TABLE 13-7. DIRECT CONTRIBUTIONS OF AIR LEAD TO BLOOD LEAD IN CHILDREN AT FIXED INPUTS OF FOOD AND WATER LEAD

Air Lead ($\mu g/m^3$)	PbB (Air)[a]	PbB (Food)[b]	PbB (Water)[c]	% PbB From Air
0.1	0.2	16.0	0.6	1.2
0.5	1.0	16.0	0.6	5.7
1.0	2.0	16.0	0.6	10.8
1.5	3.0	16.0	0.6	15.3
2.5	5.0	16.0	0.6	23.1

[a] $\frac{\Delta \text{ PbB}}{\Delta \text{ Pb Air}} = 2.0$ for 3.2 $\mu g/m^3$ or less.

[b] Assuming 100 µg Pb/day based upon Ryu et al. (1983).

[c] Assuming 10 µg Pb/l water, using Pocock et al. (1983).

TABLE 13-8. CONTRIBUTIONS OF DUST/SOIL LEAD TO BLOOD LEAD IN CHILDREN AT FIXED INPUTS OF AIR, FOOD, AND WATER LEAD

Dust-Soil (µg/g)	Air Lead µg/m^3	PbB (Air)[a]	PbB (Food)[b]	PbB (Water)[c]	PbB (Dust-Soil)[d]	% PbB From Dust/Soil
500	0.5	1.0	16.0	0.6	0.3/3.4	1.7/16.2
1000	0.5	1.0	16.0	0.6	0.6/6.8	3.3/27.8
2000	0.5	1.0	16.0	0.6	1.2/13.6	6.4/43.6

[a] $\frac{\Delta \text{ PbB}}{\Delta \text{ Pb Air}} = 2.0$ for 3.2 µg/m^3 or less.

[b] Assuming 100 µg Pb/day based on Ryu et al. (1983).

[c] Assuming 10 µg Pb/l water, based on Pocock et al. (1983).

[d] Based on range 0.6 to 6.8 µg/dl for 1000 µg/g (Angle and McIntire, 1979).

13.5 BIOLOGICAL EFFECTS OF LEAD RELEVANT TO THE GENERAL HUMAN POPULATION

13.5.1 Introduction

It is clear from the wealth of available literature reviewed in Chapter 12, that there exists a continuum of biological effects associated with lead across a broad range of exposure. At rather low levels of lead exposure, biochemical changes, e.g., disruption of certain enzymatic activities involved in heme biosynthesis and erythropoietic pyrimidine metabolism, are detectable. Heme biosynthesis is a generalized process in mammalian species, including man, with importance for normal physiological functioning of virtually all organ systems. With increasing lead exposure, there are sequentially more intense effects on heme synthesis and a broadening of lead effects to additional biochemical and physiological mechanisms in various tissues, such that increasingly more severe disruption of the normal functioning of many different organ systems becomes apparent. In addition to heme biosynthesis impairment at relatively low levels of lead exposure, disruption of normal functioning of the erythropoietic and the nervous systems are among the earliest effects observed as a function of increasing lead exposure. With increasingly intense exposure, more severe disruption of the erythropoietic and nervous systems occur and additional organ systems are affected so as to result, for example, in the manifestation of renal effects, disruption of reproductive functions, and impairment of immunological functions. At sufficiently high levels of exposure, the damage to the nervous system and other effects can be severe enough to result in death or, in some cases of non-fatal lead poisoning, long-lasting sequelae such as permanent mental retardation.

As discussed in Chapter 12 of this document, numerous new studies, reviews, and critiques concerning Pb-related health effects have been published since the issuance of the earlier EPA lead criteria document in 1977. Of particular importance for present criteria development purposes are those new findings, taken together with information earlier available at the writing of the 1977 Criteria Document, which have bearing on the establishment of quantitative dose-effect or dose-response relationships for biological effects of lead potentially viewed as adverse health effects likely to occur among the general population at or near existing ambient air concentrations of lead in the United States. Key information regarding observed health effects and their implications are discussed below for adults and children.

For the latter group, children, emphasis is placed on the discussion of (1) heme biosynthesis effects, (2) certain other biochemical and hematological effects, and (3) the disruption of nervous system functions. All of these appear to be among those effects of most concern for potential occurrence in association with exposure to existing U.S. ambient air lead levels of the population group (i.e., children ≤6 years old) at greatest risk for lead-induced health effects. Emphasis is also placed on the delineation of internal lead exposure levels, as defined mainly by blood-lead (PbB) levels, likely associated with the occurrence of such

effects. Also discussed are characteristics of the subject effects that are of crucial importance in regard to the determination of which might reasonably be viewed as constituting "adverse health effects" in affected human populations.

Over the years, there has been superimposed on the continuum of lead-induced biological effects various judgments as to which specific effects observed in man constitute "adverse health effects". Such judgments involve not only medical concensus regarding the health significance of particular effects and their clinical management, but also incorporate societal value judgments. Such societal value judgments often vary depending upon the specific overall contexts to which they are applied, e.g., in judging permissible exposure levels for occupational versus general population exposures to lead. For some lead exposure effects, e.g., severe nervous system damage resulting in death or serious medical sequelae consequent to intense lead exposure, there exists little or no disagreement as to these being significant "adverse health effects." For many other effects detectable at sequentially lower levels of lead exposure, however, the demarcation lines as to which effects represent adverse health effects and the lead exposure levels at which they are accepted as occurring are neither sharp nor fixed, having changed markedly during the past several decades. That is, from a historical perspective, levels of lead exposure deemed to be acceptable for either occupationally exposed persons or the general population have been steadily revised downward as more sophisticated biomedical techniques have revealed formerly unrecognized biological effects and concern has increased in regard to the medical and social significance of such effects.

It is difficult to provide a definitive statement of all criteria by which specific biological effects associated with any given agent can be judged to be "adverse health effects". Nevertheless, several criteria are currently well-accepted as helping to define which effects should be viewed as "adverse". These include: (1) impaired normal functioning of a specific tissue or organ system itself; (2) reduced reserve capacity of that tissue or organ system in dealing with stress due to other causative agents; (3) the reversibility/irreversibility of the particular effect(s); and (4) the cumulative or aggregate impact of various effects on individual organ systems on the overall functioning and well-being of the individual.

Examples of possible uses of such criteria in evaluating lead effects can be cited for illustrative purposes. For example, impairment of heme synthesis intensifies with increasing lead exposure until hemeprotein synthesis is inhibited in many organ systems, leading to reductions in such functions as oxygen transport, cellular energetics, and detoxification of xenobiotic agents. The latter effect can also be cited as an example of reduced reserve capacity pertinent to consideration of effects of lead, the reduced capacity of the liver to detoxify certain drugs or other xenobiotic agents resulting from lead effects on hepatic detoxification enzyme systems.

In regard to the issue of reversibility/irreversibility of lead effects, there are really two dimensions to the issue that need to be considered, i.e.: (1) biological reversibility or irreversibility characteristic of the particular effect in a given organism; and (2) the generally less-recognized concept of exposure reversibility or irreversibility. Severe central nervous system damage resulting from intense, high level lead exposure is generally accepted as an irreversible effect of lead exposure; the reversibility/irreversibility of certain more difficult-to-detect neurological effects occurring at lower lead exposure levels, however, remains a matter of some controversy. The concept of exposure reversibility/irreversibility can be illustrated by the case of urban children of low socioecomomic status showing disturbances in heme biosynthesis and erythropoiesis. Biologically, these various effects may be considered reversible; the extent to which actual reversibility occurs, however, is determined by the feasibility of removing these subjects from their particular lead exposure setting. If such removal from exposure is unlikely or does not occur, then such effects will logically persist and, defacto, constitute essentially irreversible effects.

13.5.2 Dose-Effect Relationships for Lead-Induced Health Effects

13.5.2.1 Human Adults

Table 13-9 concisely summarizes the lowest observed effect levels (in terms of blood lead concentrations) thus far credibly associated with particular health effects of concern for human adults in relation to specific organ systems or generalized physiological processes, e.g. heme synthesis.

The most serious effects associated with markedly elevated blood lead levels are severe neurotoxic effects that include irreversible brain damage as indexed by the occurrence of acute or chronic encephalopathic symptoms observed in both humans and experimental animals. For most human adults, such damage typically does not occur until blood lead levels exceed 100-120 µg/dl. Often associated with encephalopathic symptoms at such blood lead levels or higher are severe gastrointestinal symptoms and objective signs of effects on several other organ systems as well. The precise threshold for occurrence of overt neurological and gastrointestinal signs and symptoms of lead intoxication remains to be established but such effects have been observed in adult lead workers at blood lead levels as low as 40-60 µg/dl, notably lower than the 60 or 80 µg/dl levels previously established or discussed as being "safe" for occupational lead exposure.

Other types of health effects occur coincident with the above overt neurological and gastrointestinal symptoms indicative of marked lead intoxication. These range from frank peripheral neuropathies to chronic renal nephropathy and anemia. Toward the lower range of blood lead levels associated with overt lead intoxication or somewhat below, less severe but important signs of impairment in normal physiological functioning in several organ systems are evident, including: (1) slowed nerve conduction velocities indicative of peripheral nerve

TABLE 13-9. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN ADULTS

Lowest Observed Effect Level (PbB)	Heme Synthesis and Hematological Effects	Neurological Effects	Renal System Effects	Reproductive Function Effects	Gastrointestinal Effects
100-120 µg/dl		Encephalopathic signs and symptoms	Chronic renal nephropathy		Overt gastrointestinal symptoms (colic, etc.)
80 µg/dl	Frank anemia				
60 µg/dl		?			
50 µg/dl	Reduced hemoglobin production	Overt subencephalopathic neurological symptoms		Altered testicular function	
40 µg/dl	Increased urinary ALA and elevated coproporphyrins	?			
30 µg/dl		Peripheral nerve dysfunction (slowed nerve conduction)			
25-30 µg/dl	Erythrocyte protoporphyrin (EP) elevation in males	?			
15-20 µg/dl	Erythrocyte protoporphyrin (EP) elevation in females				
<10 µg/dl	ALA-D inhibition				

Abbreviations: PbB = blood lead concentrations.

dysfunction (at 30-40 μg/dl, or possibly lower levels); (2) altered testicular function (at 40-50 μg/dl); and (3) reduced hemoglobin production (at approximately 50 μg/dl) and other signs of impaired heme synthesis evident at still lower blood lead levels. All of these effects point toward a generalized impairment of normal physiological functioning across several different organ systems, which becomes abundantly evident as adult blood lead levels approach or exceed 30-40 μg/dl. Evidence for impaired heme synthesis effects in blood cells exists at still lower blood lead levels in human adults and the significance of this and evidence of impairment of other biochemical processes important in cellular energetics are the subject of discussion below in relation to health effects observed in children.

13.5.2.2 Children

Table 13-10 summarizes lowest observed effect levels for a variety of imporatnt health effects observed in children. Again, as for adults, it can be seen that lead impacts many different organ systems and biochemical/physiological processes across a wide range of exposure levels. Also, again, the most serious of these effects is the severe, irreversible central nervous system damage manifested in terms of encephalopathic signs and symptoms. In children, effective blood lead levels for producing encephalopathy or death are lower than for adults, starting at approximately 80-100 μg/dl. Other overt neurological symptoms are evident at somewhat lower blood lead levels associated with lasting neurological sequalae. Colic and other overt gastrointestinal symptoms clearly occur at similar or still lower blood lead levels in children, at least down to 60 μg/dl and, perhaps, below. Renal dysfunction is also manifested along with the above overt signs of lead intoxication in children and has been reported at blood lead levels as low as 40 μg/dl in some pediatric populations. Frank anemia is also evident at 70 μg/dl, representing an extreme manifestation of reduced hemoglobin synthesis observed at blood lead levels as low as 40 μg/dl along with other signs of marked heme synthesis inhibition at that exposure level. Again, all of these effects are reflective of widespread impact of lead on the normal physiological functioning of many different organ systems in children at blood lead levels at least as low as 40 μg/dl.

Among the most important and controversial of the issues discussed in Chapter 12 are the evaluation of neuropsychological or electrophysiological effects associated with low-level lead exposures in non-overtly lead intoxicated children. None of the available studies on the subject, individually, can be said to prove conclusively that significant neurological effects occur in children at blood-Pb levels <30 μg/dl. The collective neurobehavioral studies of CNS (cognitive; IQ) effects, for example, can probably now be most reasonably interpreted as most clearly being indicative of a likely association between neuropsychologic deficits and low-level Pb-exposures in young children resulting in blood-Pb levels of approximately 30 to 50 μg/dl.

TABLE 13-10. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN CHILDREN

Lowest Observed Effect Level (PbB)	Heme Synthesis and Hematological Effects	Neurological Effects	Renal System Effects	Gastrointestinal Effects	Other Biochemical Effects
80-100 µg/dl		Encephalopathic signs and symptoms	Renal dysfunction (aminoaciduria)	Colic, other overt gastrointestinal symptoms	
70 µg/dl	Frank anemia		↓	↓	
60 µg/dl		↕			
50 µg/dl		?			
40 µg/dl	Reduced hemoglobin	Cognitive (CNS) deficts			
	Elevated coproporphyrin	Peripheral nerve dysfunction (slowed NCV's)			
	Increased urinary ALA	↓			
30 µg/dl		↕			Vitamin D metabolism interference
15-20 µg/dl	Erythrocyte protoporphyin elevation	CNS electrophysiological deficits			
10	ALA-D inhibition	?			Py-5-N activity inhibition
	↓				
	?				

Abbreviations: PbB = blood lead concentrations; Py-5-N = pyrimidine-5'-nucleotidase.

However, due to specific methodological problems with each of the various studies (as noted in Chapter 12), much caution is warranted that precludes conclusive acceptance of the observed effects being due to Pb rather than other (at times uncontrolled for) potentially confounding variables.

Also of considerable importance are studies by by Benignus et al. (1981) and Otto et al. (1981, 1982a,b), which provide evidence of changes in EEG brain wave patterns and CNS evoked potential responses in non-overtly lead intoxicated children experiencing relatively low blood-Pb levels. Sufficient exposure information was provided by Otto et al. (1981, 1982a,b); and appropriate statistical analyses were carried out which demonstrated clear, statistically significant associations between electrophysiological (SW voltage) changes and blood-Pb levels in the range of 30 to 55 μg/dl and probable analogous associations at blood-Pb levels below 30 μg/dl (with no evident threshold down to 15 μg/dl). In this case, the continued presence of such electrophysiological changes upon follow-up two years later, suggests persistence of such effects even in the face of later declines in blood-Pb levels and, therefore, possible non-reversibility of the observed electrophysiological CNS changes. However, the reported electrophysiological effects were not found to be significantly associated with IQ decrements.

The precise medical or health significance of the neuropsychological and electrophysiological effects found by the above studies to be associated with low-level Pb-exposures is difficult to state with confidence at this time. The IQ deficits and other behavioral changes, although statistically significant, are generally relatively small in magnitude as detected by the reviewed studies, but nevertheless may still impact the intellectual development, school performance, and social development of the affected children sufficiently so as to be regarded as adverse. This would be especially true if such impaired intellectual development or school performance and disrupted social development were reflective of persisting, long-term effects of low-level lead exposure in early childhood. The issue of persistence of such lead effects, however, remains to be more clearly resolved, with some study results reviewed in Chapter 12 and mentioned above suggesting relatively short-lived or markedly decreasing Pb-effects on neuropsychological functions over a few years from early to later childhood and other studies suggesting that significant low-level Pb-induced neurobehavioral and EEG effects may, in fact, persist into later childhood.

In regard to additional studies reviewed in Chapter 12 concerning the neurotoxicity of lead, certain evidence exists which suggests that neurotoxic effects may be associated with Pb-induced altered heme synthesis, which results in an accumulation of ALA in brain affecting CNS GABA synthesis, binding, and/or inactivation by neuronal reuptake after synaptic release. Also, available experimental data suggest that these effects may have functional significance in the terms of this constituting one mechanism by which lead may increase the sensitivity of

rats to drug-induced seizures and, possibly, by which GABA-related behavioral or physiological control functions are disrupted. Unfortunately, the available research data do not allow credible direct estimates of blood-Pb levels at which such effects might occur in rats, other non-human mammalian species, or man. Inferentially, however, one can state that threshold levels for any marked Pb-induced ALA impact on CNS GABA mechanisms are most probably at least as high as blood-Pb levels at which significant accumulations of ALA have been detected in erythrocytes or non-blood soft tissues (see below). Regardless of any dose-effect levels inferred, though, the functional and/or medical significance of Pb-induced ALA effects on CNS mechanisms at low-levels of Pb-exposure remains to be more fully determined and cannot, at this time, be unequivocably seen as an adverse health effect.

Research concerning Pb-induced effects on heme synthesis, also provides information of importance in evaluating whether significant health effects in children are associated with blood-Pb levels below 30 µg/dl. As discussed earlier, in Chapter 12, Pb affects heme synthesis at several points in its metabolic pathway, with consequent impact on the normal functioning of many body tissues. The activity of the enzyme, ALA-S, catalyzing the rate-limiting step of heme synthesis does not appear to be significantly affected until blood-Pb levels reach or exceed approximately 40 µg/dl. The enzyme ALA-D, which catalizes the conversion of ALA to porphobilinogen as a further step in the heme biosynthetic pathway, appears to be affected at much lower blood-Pb levels as indexed directly by observations of ALA-D inhibition or indirectly in terms of consequent accumulations of ALA in blood and non-blood tissues. More specifically, inhibition of erythrocyte ALA-D activity has been observed in humans and other mammalian species at blood-Pb levels even below 10 to 15 µg/dl, with no clear threshold evident. Correlations between erythrocyte and hepatic ALA-D activity inhibition in lead workers at blood-Pb levels in the range of 12 to 56 µg/dl suggest that ALA-D activity in soft tissues (eg. brain, liver, kidney, etc.) may be inhibited at similar blood-Pb levels at which erythrocyte ALA-D activity inhibition occurs, resulting in accumulations of ALA in both blood and soft tissues.

It is now clear that significant increases in both blood and urinary ALA occur below the currently commonly-accepted blood-Pb level of 40 µg/dl and, in fact, such increases in blood and urinary ALA are detectable in humans at blood-Pb levels below 30 µg/dl, with no clear threshold evident down to 15 to 20 µg/dl. Other studies have demonstrated significant elevations in rat brain, spleen and kidney ALA levels consequent to acute or chronic Pb-exposure, but no clear blood-Pb levels can yet be specified at which such non-blood tissue ALA increases occur in humans. It is reasonable to assume, however, that ALA increases in non-blood tissues likely begin to occur at roughly the same blood-Pb levels associated with increases in erythrocyte ALA levels.

Lead also affects heme synthesis beyond metabolic steps involving ALA, leading to the accumulation of protoporphyrin in erythrocytes as the result of impaired iron insertion into the porphyrin moiety to form heme. The porphyrin acquires a zinc ion in lieu of the native iron, and the resulting accumulation of blood zinc protoporphyrin (ZPP) tightly bound to erythrocytes for their entire life (120 days) represents a commonly employed index of Pb-exposure for medical screening purposes. The threshold for elevation of erythrocyte protoporphyrin (EP) levels is well-established as being 25 to 30 μg/dl in adults and approximately 15 μg/dl for young children, with significant EP elevations (>1 to 2 standard deviations above reference normal EP mean levels) occurring in 50 percent of all children studied as blood-Pb approaches or moderately exceeds 30 μg/dl.

Medically, small increases in EP levels have generally not been viewed as being of great concern at initial detection levels around 15 to 20 μg/dl in children, but EP increases become more worrisome as markedly greater, significant EP elevations occur as blood-Pb levels approach and exceed 30 μg/dl and additional signs of significantly deranged heme synthesis begin to appear along with indications of functional disruption of various organ systems. Previously, such other signs of significant organ system functional disruptions had only been credibly detected at blood-Pb levels somewhat in excess of 30 μg/dl, e.g., hemoglobin synthesis inhibition starting at 40 μg/dl and significant nervous system effects at 50-60 μg/dl. This served as a basis for CDC establishment of 30 μg/dl blood-Pb as a criteria level for undue Pb exposure for young children and adoption by EPA of it as the "maximum safe" blood-Pb level (allowing some margin(s) of safety before reaching levels associated with inhibition of hemoglobin synthesis or nervous system deficits) in setting the 1978 NAAQS for lead.

To the extent that new evidence is now available, indicative of probable Pb effects on nervous system functioning or other important physiological processes at blood-Pb levels below 30 to 40 μg/dl, then the rationale for continuing to view 30 μg/dl as a "maximum safe" blood-Pb level is called into question and substantial impetus is provided for revising the criteria level downward, i.e., to some blood-Pb level below 30 μg/dl. At this time, such impetus toward revising the blood-Pb criteria level downward is gaining momentum not only from new neuropsychologic and electrophysiological findings of the type summarized above, but also from growing evidence for Pb effects on other functional systems. These include, for example, the: (1) disruption of formation of the heme-containing protein, cytochrome c, of considerable importance in cellular energetics involved in mediation of the normal functioning of many different mammalian (including human) organ systems and tissues; (2) inhibition by Pb of the biosynthesis of globin, the protein moiety of hemoglobin, in the presense of Pb at concentrations corresponding to a blood-Pb level of 20 μg/dl; (3) observations of significant inhibition of pyrimidine-5'-nucleotidase (Py-5-N) activity in adults at blood-Pb levels ≧44 μg/dl and in

children down to blood-Pb levels of 10 µg/dl; and (4) observations of Pb interference with vitamin D metabolism in children across a blood-Pb level range of 33 to 120 µg/dl, with consequent increasingly enhanced Pb uptake due to decreased vitamin D metabolism and likely associated increasingly cascading effects on nervous system and other functions at sequentially higher blood-Pb levels. Certain additional evidence for Pb effects on hormonal systems and immune system components, thus far detected only at relatively high blood-Pb levels or at least not credibly associated with blood-Pb levels as low as 30 to 40 µg/dl, also contributes to concern as blood-Pb levels exceed 30 µg/dl.

Also adding to the concern about relatively low lead exposure levels are the results of an expanding array of animal toxicology studies which demonstrate: (1) persistence of lead-induced neurobehavioral alterations well into adulthood long after termination of perinatal lead exposure early in development of several mammalian species; (2) evidence for uptake and retention of lead in neural and non-neuronal elements of the CNS, including long-term persistence in brain tissues after termination of external lead exposure and blood lead levels return to "normal"; and (3) evidence from various in-vivo and in-vitro studies indicating that, at least on a subcellular-molecular level, no threshold may exist for certain neurochemical effects of lead.

13.6 DOSE-RESPONSE RELATIONSHIPS FOR LEAD EFFECTS IN HUMAN POPULATIONS

Information summarized in the preceding section dealt with the various biological effects of lead germane to the general population and included comments about the various levels of blood lead observed to be associated with the measurable onset of these effects in various populations groups.

As indicated above, inhibition of ALA-D activity by lead occurs at virtually all blood lead levels measured in subjects residing in industrialized countries. If any threshold for ALA-D inhibition exists, it lies somewhere below 10 µg Pb/dl in blood lead.

Elevation in erythrocyte porphyrin for a given blood lead level is greater in children and women than in adult males, children being somewhat more sensitive than women. The threshold for currently detectable EP elevation in terms of blood lead levels for children was estimated at ca. 16 to 17 µg/dl in the recent studies of Piomelli et al. (1982). In adult males, the corresponding blood lead value is 25 to 30 µg/dl.

Statistically significant reduction in hemoglobin production occurs at a lower blood lead level in children, 40 µg/dl, than in adults, 50 µg/dl.

It appears that urinary ALA shows a correlation with blood lead levels to below 40 µg/dl, but since there is no clear agreement as to the meaning of elevated ALA-U below 40 µg/dl, this

value is taken as the threshold for pronounced excretion of ALA into urine. This value appears to apply to both children and adults. Whether this blood lead level represents a threshold for the potential neurotoxicity of circulating ALA cannot now be stated and requires further study.

Coproporphyrin elevation in urine first occurs at a blood lead level of 40 µg/dl and this threshold appears to apply for both children and adults.

A number of investigators have attempted to quantify more precisely dose-population response relationships for some of the above lead effects in human populations. That is they have attempted to define the proportion of a population exhibiting a particular effect at a given blood lead level. To date, such efforts at defining dose-response relationships for lead effects have been mainly limited to the following effects of lead on heme biosynthesis: inhibition of ALA-D activity; elevation of EP; and urinary excretion of ALA.

Dose-population response relationships for EP in children has been analyzed in detail by Piomelli and et al. (1982) and the corresponding plot at 2 levels of elevation (>1 S.D., >2 S.D.) is shown in Figure 13-3 using probit analysis. It can be seen that blood lead levels in half of the children showing EP elevations at >1 and 2 S.D.'s closely bracket the blood lead level taken as the high end of "normal" (i.e., 30 µg/dl). Dose-response curves for adult men and women as well as children prepared by Roels et al. (1976) are set forth in Figure 13-4. In Figure 13-4, it may be seen that the dose-response for children remains greater across the blood-lead range studied, followed by women, then adult males.

Figure 13-5 presents dose-population response data for urinary ALA exceeding two levels (at mean + 1 S.D. and mean + 2 S.D.), as calculated by EPA from the data of Azar et at. (1975). The percentages of the study populations exceeding the corresponding cut-off levels as calculated by EPA for the Azar data are set forth in Table 13-11. It should be noted that the measurement of ALA in the Azar et al. study did not account for amino acetone, which may influence the results observed at the lowest blood lead levels.

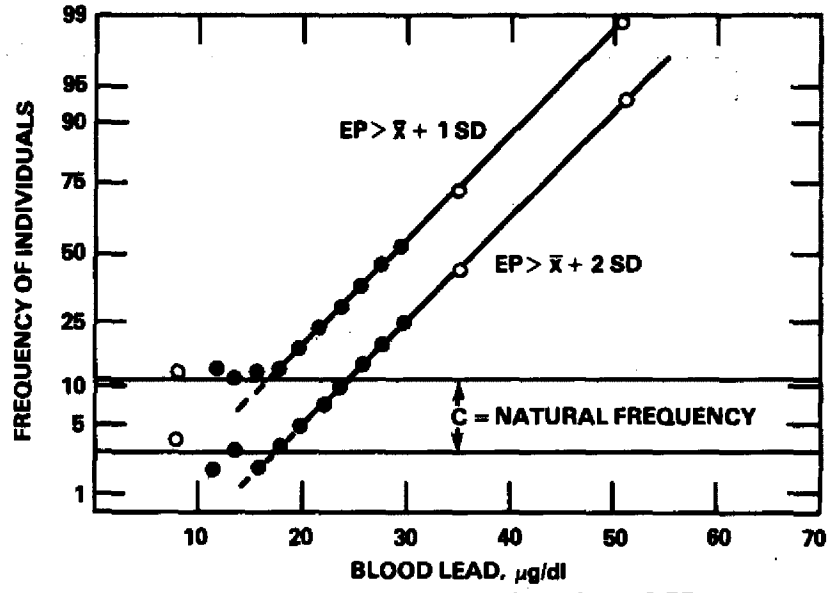

Figure 13-3. Dose-response for elevation of EP as a function of blood lead level using probit analysis. Geometric mean plus 1 S.D. = 33 μg/dl; geometric mean plus 2 S.D. = 53 μg/dl.

Source: Piomelli et al. (1982).

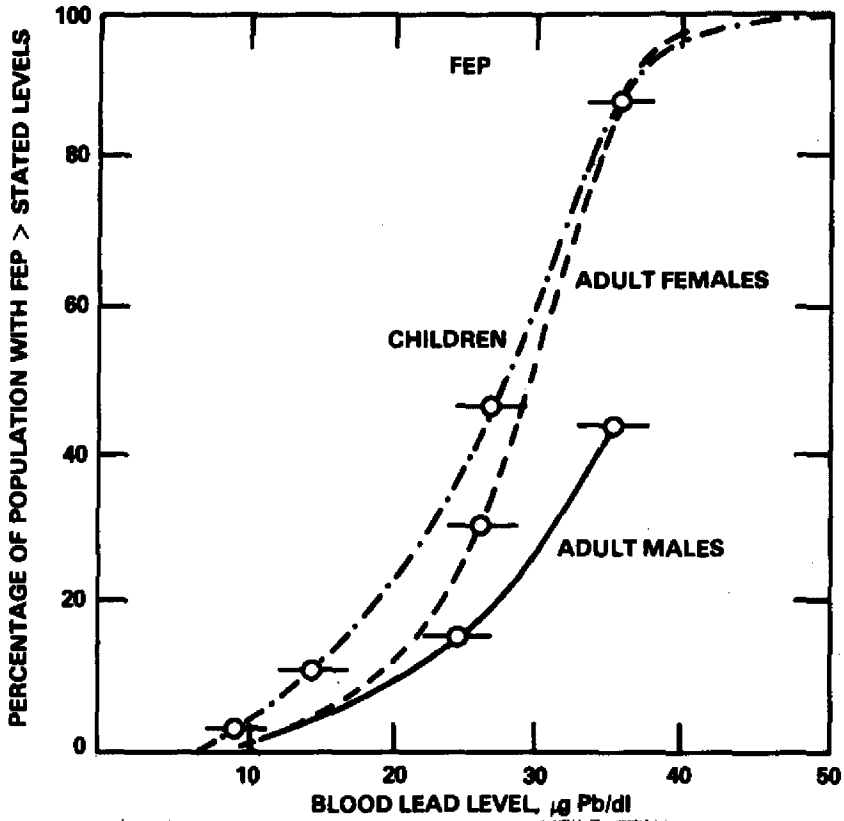

Figure 13-4. Dose-response curve for FEP as a function of blood lead level: in subpopulations.

Source: Roels et al. (1976).

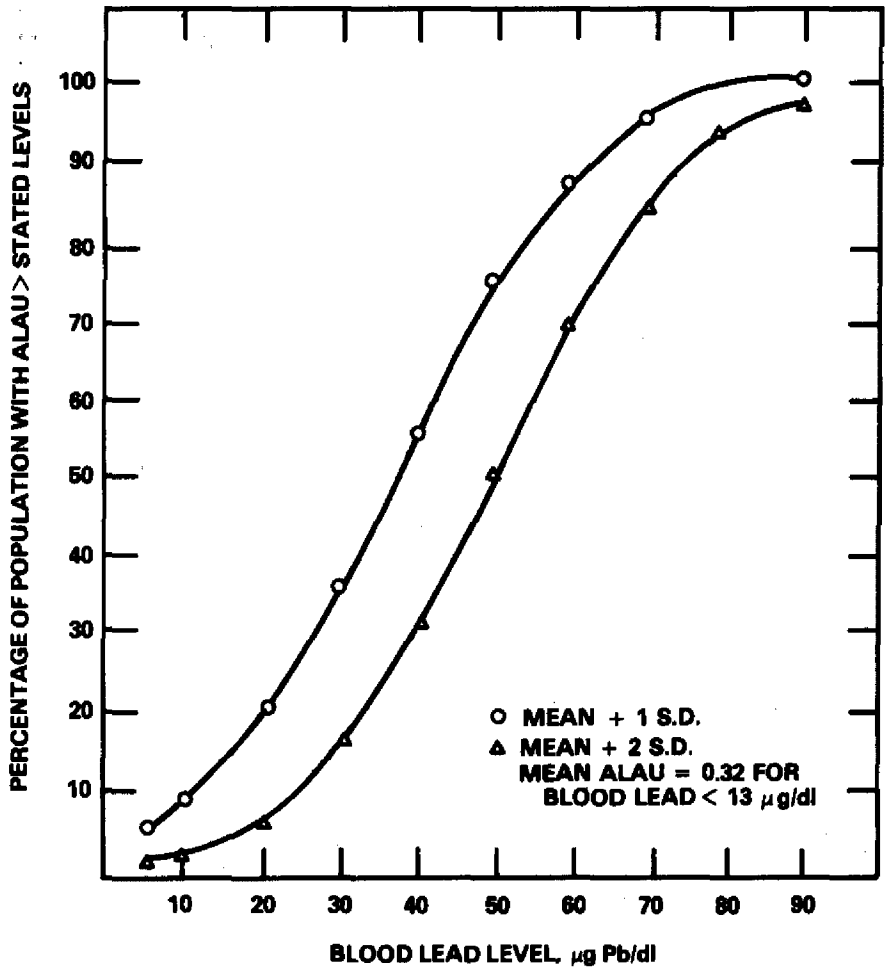

Figure 13-5. EPA calculated dose-response curve for ALA-U.

Source: Azar et al. (1975).

TABLE 13-11. EPA-ESTIMATED PERCENTAGE OF SUBJECTS WITH ALA-U EXCEEDING LIMITS FOR VARIOUS BLOOD LEAD LEVELS

Blood lead levels (μg/dl)	Azar et al. (1975) (Percent Population)
10	2
20	6
30	16
40	31
50	50
60	69
70	84

13.7 POPULATIONS AT RISK

Population at risk is a segment of a defined population exhibiting characteristics associated with significantly higher probability of developing a condition, illness, or other abnormal status. This high risk may result from either (1) greater inherent susceptibility or (2) from exposure situations peculiar to that group. What is meant by inherent susceptibility is a host characteristic or status that predisposes the host to a greater risk of heightened response to an external stimulus or agent.

In regard to lead, two such populations are definable. They are preschool age children, especially those living in urban settings, and pregnant women, the latter group owing mainly to the risk to the conceptus. Children are such a population for both of the reasons stated above, whereas pregnant women are at risk primarily due to the inherent susceptibility of the conceptus.

13.7.1 Children as a Population at Risk

Children are developing and growing organisms exhibiting certain differences from adults in terms of basic physiologic mechanisms, capability of coping with physiologic stress, and their relative metabolism of lead. Also, the behavior of children frequently places them in different relationship to sources of lead in the environment, thereby enhancing the opportunity for them to absorb lead. Furthermore, the occurrence of excessive exposure often is not realized until serious harm is done. Young children do not readily communicate a medical history of lead exposure, the early signs of such being common to so many other disease states that lead is frequently not recognized early on as a possible etiological factor contributing to the manifestation of other symptoms.

13.7.1.1 Inherent Susceptibility of the Young. Discussion of the physiological vulnerability of the young must address two discrete areas. Not only should the basic physiological differences be considered that one would expect to predispose children to a heightened vulnerability to lead, but also the actual clinical evidence must be considered that shows such vulnerability does indeed exist.

In Chapter 10 and Section 13.2 above, differences in relative exposure to lead and body handling of lead for children versus adults were pinpointed throughout the text. The significant elements of difference include: (1) greater intake of lead by infants and young children into the respiratory and gastro-intestinal tracts on a body weight basis compared to adults; (2) greater absorption and retention rates of lead in children; (3) much greater prevalence of nutrient deficiency in the case of nutrients which affect lead absorption rates from the GI tract; (4) differences in certain habits, i.e., normal hand to mouth activity as well as pica resulting in the transfer of lead-contaminated dust and dirt to the GI tract; (5) differences

in the efficiency of lead sequestration in the bones of children, such that not only is less of the body burden of lead in bone at any given time but the amount present may be relatively more labile. Additional information discussed in Chapter 12 suggests that the blood-brain barrier in children is less developed, posing the risk for greater entry of lead into the nervous system.

Hematological and neurological effects in children have been demonstrated to have lower thresholds in terms of blood lead levels than in adults. The extent of reduced hemoglobin production and EP accumulation occur at relatively lower exposure levels in children than in adults, as indexed by blood lead thresholds. With reference to neurologic effects, the onset of encephalopathy and other injury to the nervous system appears to vary both regarding likely lower thresholds in children for some effects and in the typical pattern of neurologic effects presented, e.g., in encephalopathy or other CNS deficits being more common in children versus peripheral neuropathy being more often seen in adults. Not only are the effects more acute in children than in adults, but also the neurologic sequelae are usually much more severe in children.

13.7.1.2 Exposure Consideration. The dietary habits of children as well as the diets themselves differ markedly from adults and, as a result, place children in a different relationship to several sources of lead. The dominance of canned milk and processed baby food in the diet of many young children is an important factor in assessing their exposure to lead since both those foodstuffs have been shown to contain higher amounts of lead than components of the adult diet. The importance of these lead sources is not their relationship to airborne lead directly but, rather, their role in providing a higher baseline lead burden to which the airborne contribution is added.

Children ordinarily undergo a stage of development in which they exhibit normal mouthing behavior, as manifested, for example, in the form of thumbsucking. At this time they are at risk for picking up lead-contaminated soil and dust on their hands and hence into their mouths where it can be absorbed. Scientific evidence documenting at least the first part of the chain is available.

There is, however, an abnormal extension of mouthing behavior, called pica, which occurs in some children. Although diagnosis of this is difficult, children who exhibit this trait have been shown to purposefully eat nonfood items. Much of the lead-based paint problem is known to occur because children actively ingest chips of leaded paint.

13.7.2 Pregnant Women and the Conceptus as a Population at Risk

There are some rather inconculsive data indicating that women may in general be somewhat higher risk to lead than men. However, pregnant women and their concepti as a subgroup are

demonstrably at higher risk. It should be pointed out that, in fact, it really is not the pregnant woman per se who is at greatest risk but, rather, the unborn child she is carrying. Because of obstetric complications, however, the mother herself can also be at somewhat greater risk at the time of delivery of her child.

Studies have demonstrated that women in general, like children, tend to show a heightened response of erythorcyte protoporphyrin levels upon exposure to lead. The exact reason for this heightened response is not known but may relate to endocrine differences between men and women.

As stated above, the primary reason pregnant women are a high-risk group is because of the fetus each is carrying. In addition, there is some suggestive evidence that lead exposures may also affect maternal complications at delivery. With reference to maternal complication at delivery, information in the literature suggests that the incidence of preterm delivery and premature membrane rupture relates to maternal blood lead level. Further study of this relationship as well as studies relating to discrete health effects in the newborn are needed.

Vulnerability of the developing fetus to lead exposure arising from transplacental transfer of maternal lead was discussed in Chapter 10. This process starts at the end of the first trimester. Umbilical cord blood studies involving mother-infant pairs have repeatedly shown a correlation between maternal and fetal blood lead levels.

Further suggestive evidence, cited in Chapter 12, has been advanced for prenatal lead exposures of fetuses possibly leading to later higher instances of postnatal mental retardation among the affected offspring. The available data are insufficient to state with any certainty that such effects occur or to determine with any precision what levels of lead exposure might be required prior to or during pregnancy in order to produce such effects.

13.7.3 Description of the United States Population in Relation to Potential Lead Exposure Risk

In this section, estimates are provided of the number of individuals in those segments of the population which have been defined as being potentially at greatest risk for lead exposures. These segments include pre-school children (up to 6 years of age), especially those living in urban settings, and women of child-bearing age (defined here as ages 15-44). These data, which are presented below in Table 13-12, were obtained from a provisional report by the U.S. Census Bureau (1982), which indicates that approximately 61 percent of the populace lives in urban areas (defined as central cities and urban fringe). Assuming that the 61 percent estimate for urban residents also applies to children of preschool age, then approximately 14,206,000 children of the total listed in Table 13-12 would be expected to be at greater risk

by virtue of higher lead exposures generally associated with their living in urban versus non-urban settings. (NOTE: The age distribution of the percentage of urban residents may vary between SMSA's.)

TABLE 13-12. PROVISIONAL ESTIMATE OF THE NUMBER OF INDIVIDUALS IN URBAN AND RURAL POPULATION SEGMENTS AT GREATEST POTENTIAL RISK TO LEAD EXPOSURE

Population Segment	Actual Age (year)	Total Number in U.S. Population (1981)	Urban Population[1]
Pre-school children	0-4	16,939,000	10,333,000
	5	3,201,000	1,953,000
	6	3,147,000	1,920,000
Total		23,287,000	14,206,000
Women of child-bearing age	15-19	10,015,000	6,109,000
	20-24	10,818,000	6,599,000
	25-29	10,072,000	6,144,000
	30-34	9,463,000	5,772,000
	35-39	7,320,000	4,465,000
	40-44	6,147,000	3,749,000
Total		53,835,000	32,838,000

Source: U.S. Census Bureau (1982), Tables 18 and 31.

[1]An urban/total ratio of 0.61 was used for all age groups. "Urban" includes central city and urban fringe populations.

The risk encountered with exposure to lead may be compounded by nutritional deficits (see Chapter 10). The most commonly seen of these is iron deficiency, especially in young children less than 5 years of age (Mahaffey and Michaelson, 1980). Data available from the National Center for Health Statistics for 1976-1980 (Fulwood et al., 1982) indicate that from 8 to 22 percent of children aged 3-5 may exhibit iron deficiency, depending upon whether this condition is defined as serum iron concentration (<40 μg/dl) or as transferrin saturation (<16 percent), respectively. Hence, of the 20,140,000 children ≤5 years of age (Table 13-12), as many as 4,431,000 would be expected to be at increased risk depending on their exposure to lead, due to iron deficiency.

As pointed out in Section 13.7.2, the risk to pregnant women is mainly due to risk to the conceptus. By dividing the total number of women of child-bearing age in 1981 (53,835,000) into the total number of live births in 1981 (3,646,000; National Center for Health Statistics, 1982), it may be seen that approximately 7 percent of this segment of the population may be at increased risk at any given time.

13.8 SUMMARY AND CONCLUSIONS

Among the most significant pieces of information and conclusions that emerge from the present human health risk evaluation are the following:

(1) Anthropogenic activity has clearly led to vast increases of lead input into those environmental compartments which serve as media (e.g., air, water, food, etc.) by which significant human exposure to lead occurs.

(2) Emission of lead into the atmosphere, especially through leaded gasoline combustion, is of major significance in terms of both the movement of lead to other environmental compartments and the relative impact of such emissions on the internal lead burdens in industrialized human populations. By means of both mathematical modeling of available clinical/epidemiological data by EPA and the isotopic tracing of lead from gasoline to the atmosphere to human blood of exposed populations, the size of atmospheric lead contribution can be confidently said to be 25-50 percent or probably somewhat higher.

(3) Given this magnitude of relative contribution to human external and internal exposure, reduction in levels of atmospheric lead would then result in significant widespread reductions in levels of lead in human blood (an outcome which is supported by careful analysis of the NHANES II study data). Reduction of lead in food (added in the course of harvesting, transport, and processing) would also be expected to produce significant widespread reductions in human blood lead levels in the United States.

(4) A number of adverse effects in humans and other species are clearly associated with lead exposure and, from a historical perspective, the observed "thresholds" for these various effects (particularly neurological and heme biosynthesis effects) continue to decline as more sophisticated experimental and clinical measures are employed to detect more subtle, but still significant effects. These include significant alterations in normal physiological functions at blood lead levels markedly below the currently accepted 30 μg/dl "maxim safe level" for pediatric exposures.

(5) Preceding chapters of this document demonstrate that young children are at greatest risk for experiencing lead-induced health effects, particularly in the urbanized, low income segments of this pediatric population. A second group at increased risk are pregnant women, because of exposure of the fetus to lead in the absence of any effective biological (e.g. placental) barrier during gestation.

(6) Dose-population response information for heme synthesis effects, coupled with information from various blood lead surveys, e.g. the NHANES II study, indicate that large numbers of American children (especially low income, urban dwellers) have blood lead levels sufficiently high (in excess of 15-20 μg/dl) that they are clearly at risk for deranged heme synthesis and, possibly, other health effects of growing concern as lead's role as a general systemic toxicant becomes more fully understood.

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