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Environmental Criteria and
Assessment Office
Research Triangle Park NC 27711

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Air Quality Criteria for Lead

Review Draft

(Do Not
Cite or Quote)

Volume I of IV

NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
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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

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.

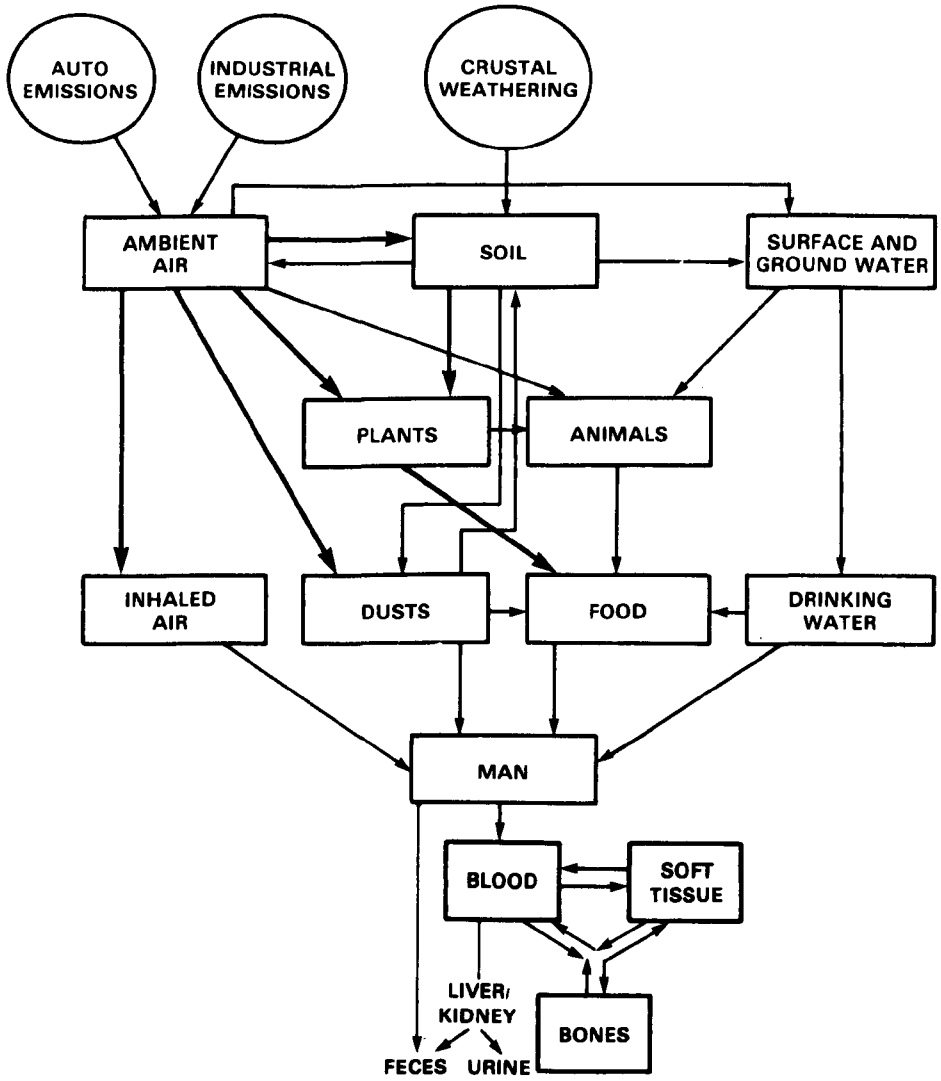

Figure 1-1. Pathways of lead exposure from the environment to man.

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.

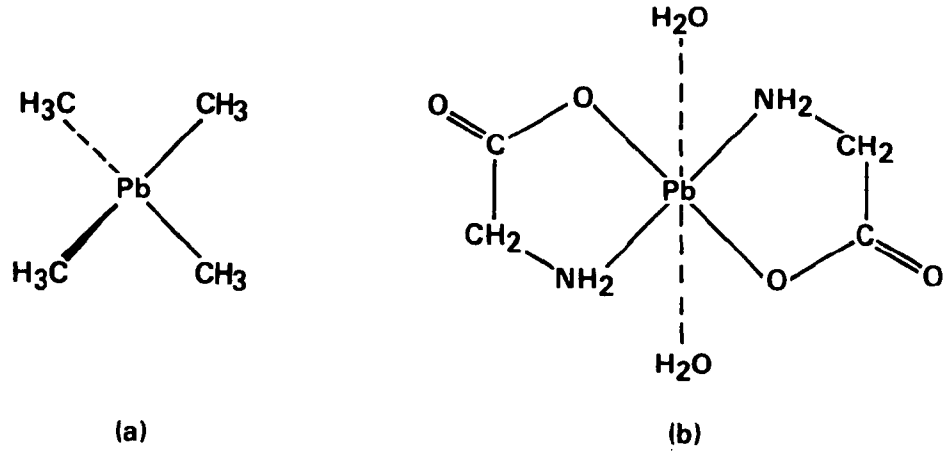

Figure 1-2. Metal complexes of lead.

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.

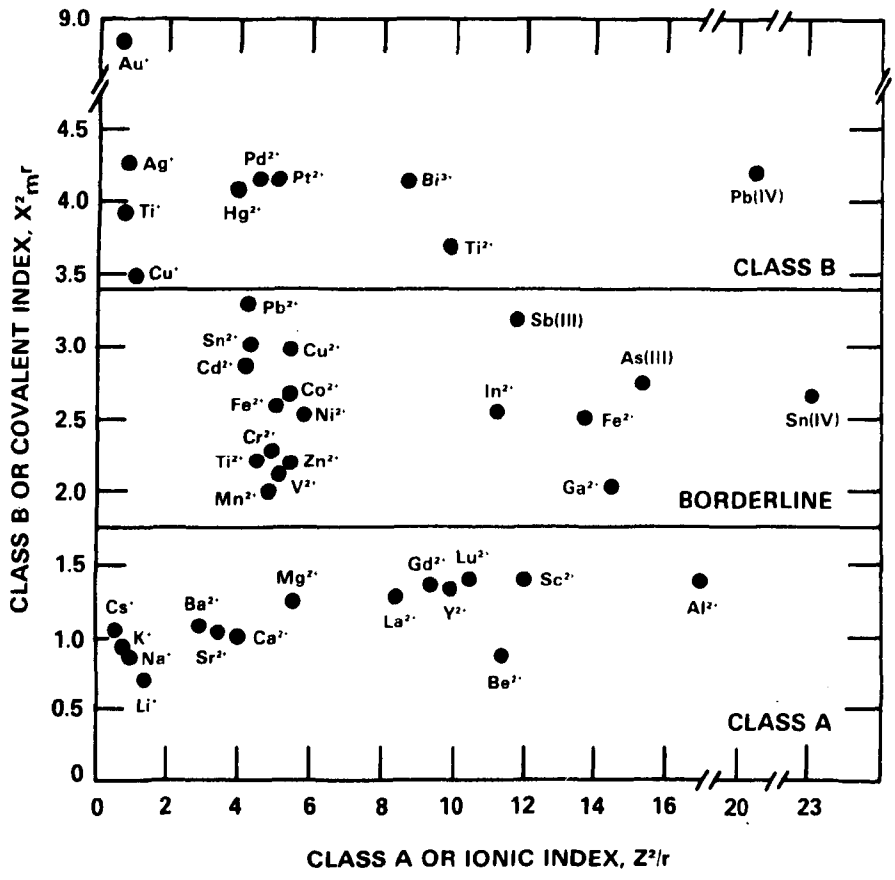

Figure 1-3. Softness parameters of metals.

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

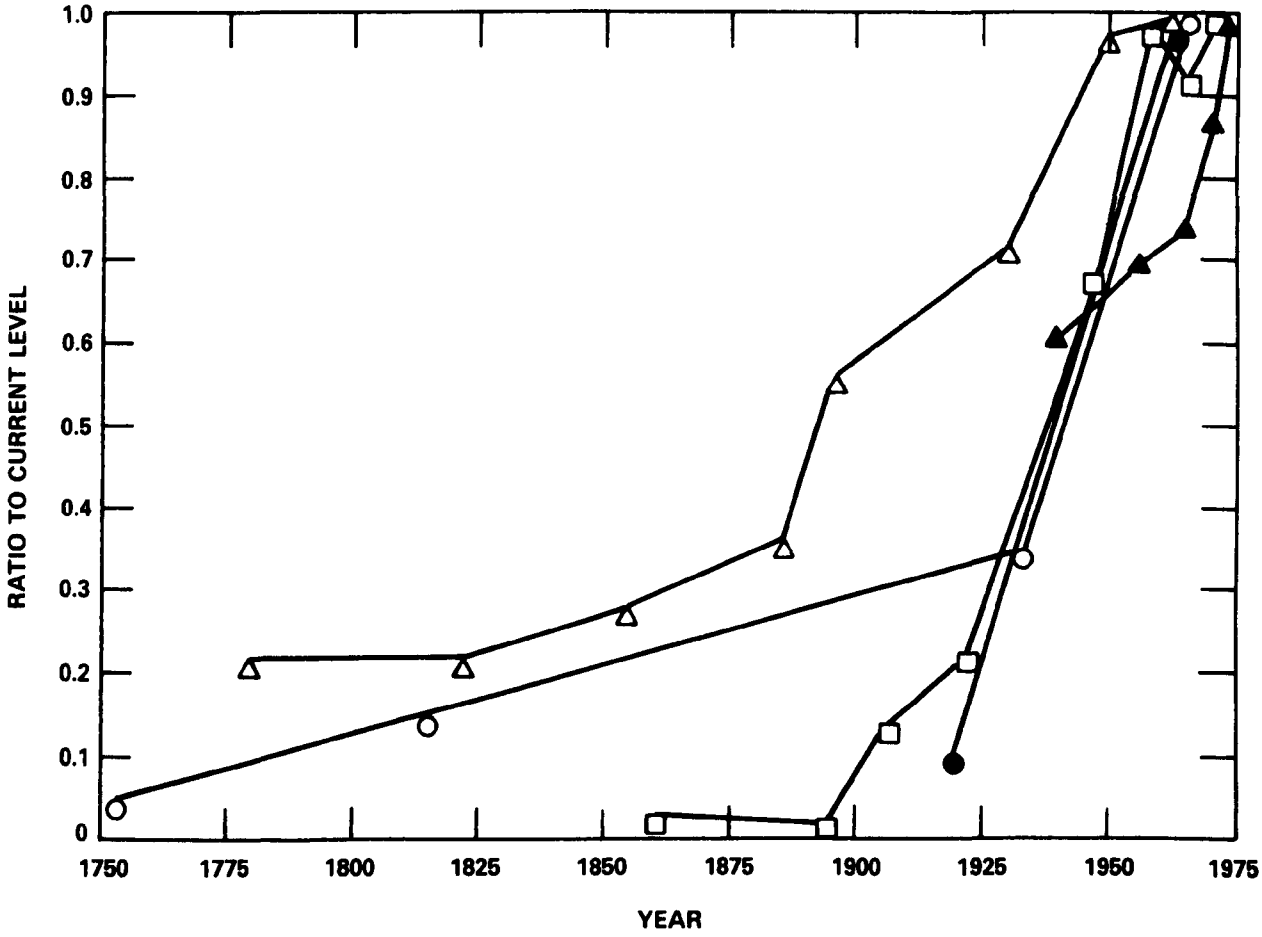

Figure 1-4. Chronological record of the relative increase of lead in snow strata, pond and lake sediments, marine sediments, and tree rings. The data are expressed as a ratio of the latest year of the record and should not be interpreted to extend back in time to natural or uncontaminated levels of lead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

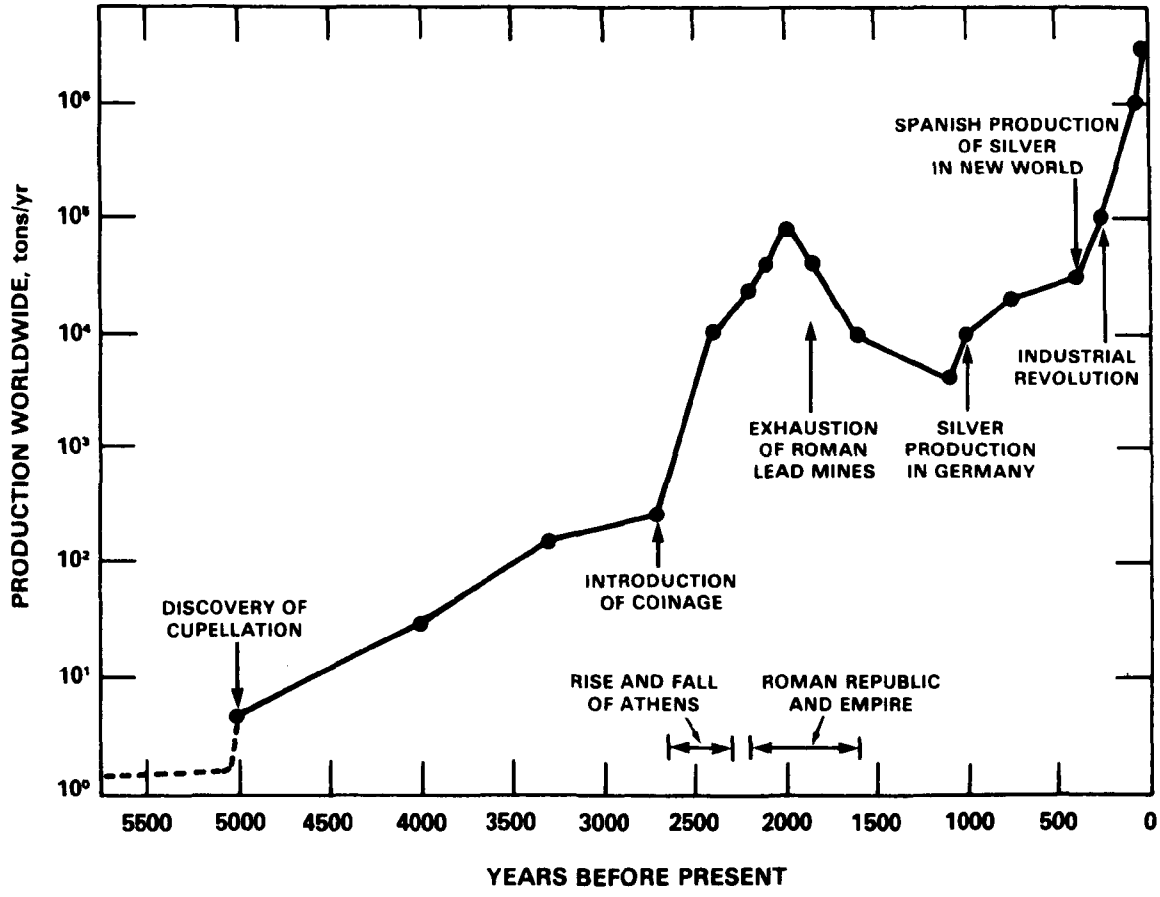

Figure 1-5. The global lead production has changed historically in response to major economic and political events. Increases in lead production (note log scale) correspond approximately to historical increases in lead emissions shown in Figure 5-1.

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

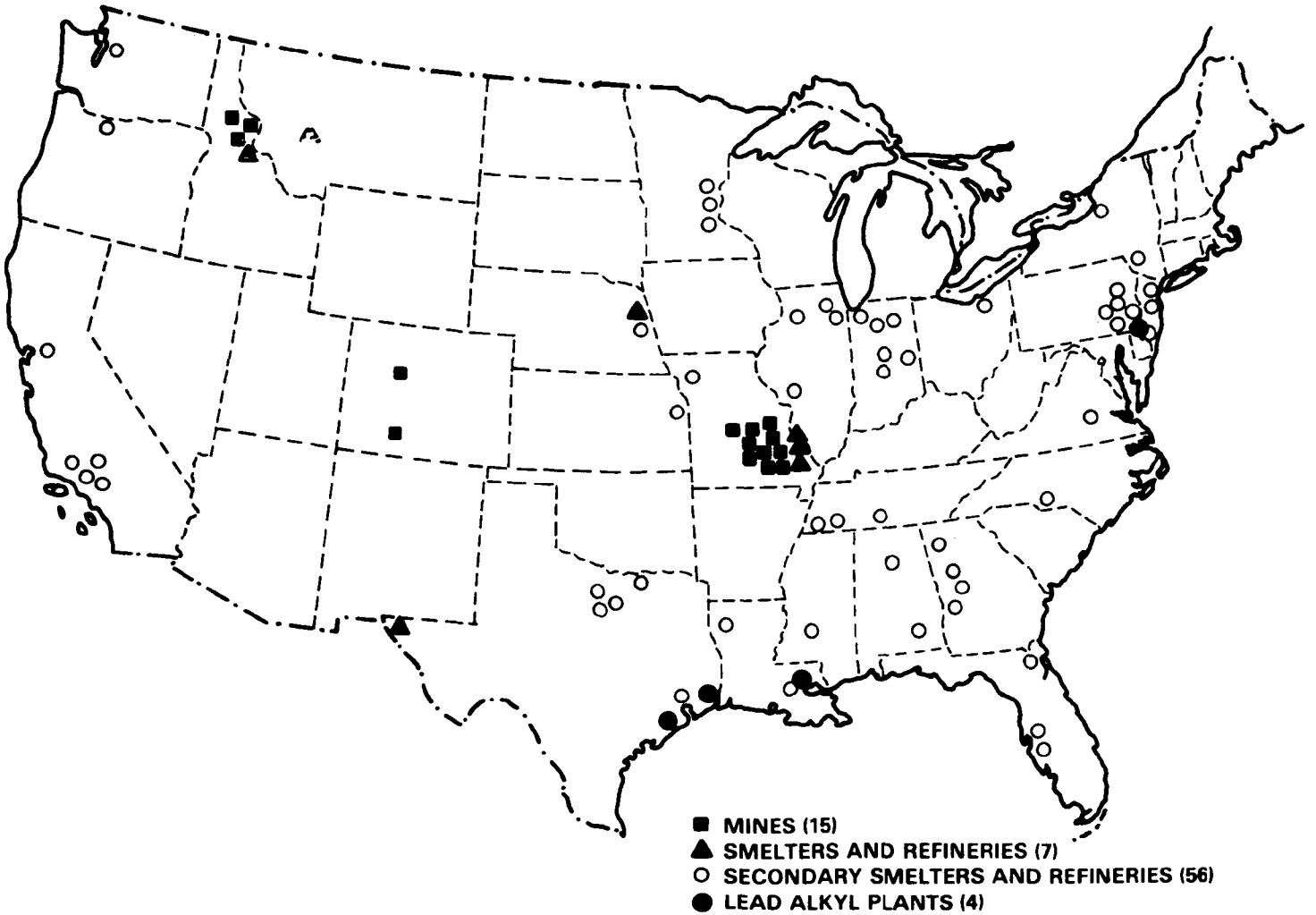

Figure 1-6. Locations of major lead operations in the United States.

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.

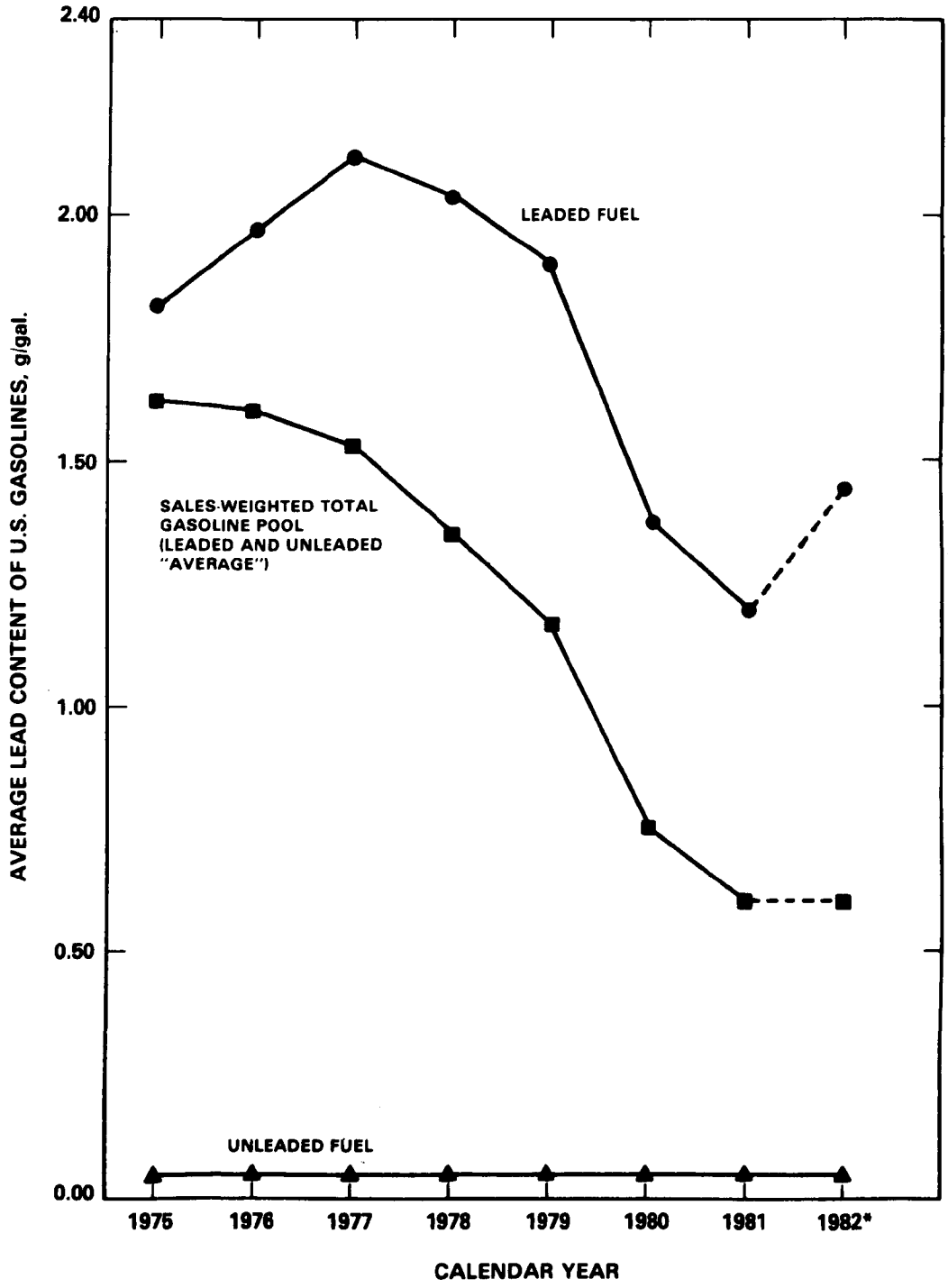

Figure 1-7. Trend in lead content of U.S. gasolines, 1975-1982. (DuPont, 1982).

***1982 DATA ARE FORECASTS.**

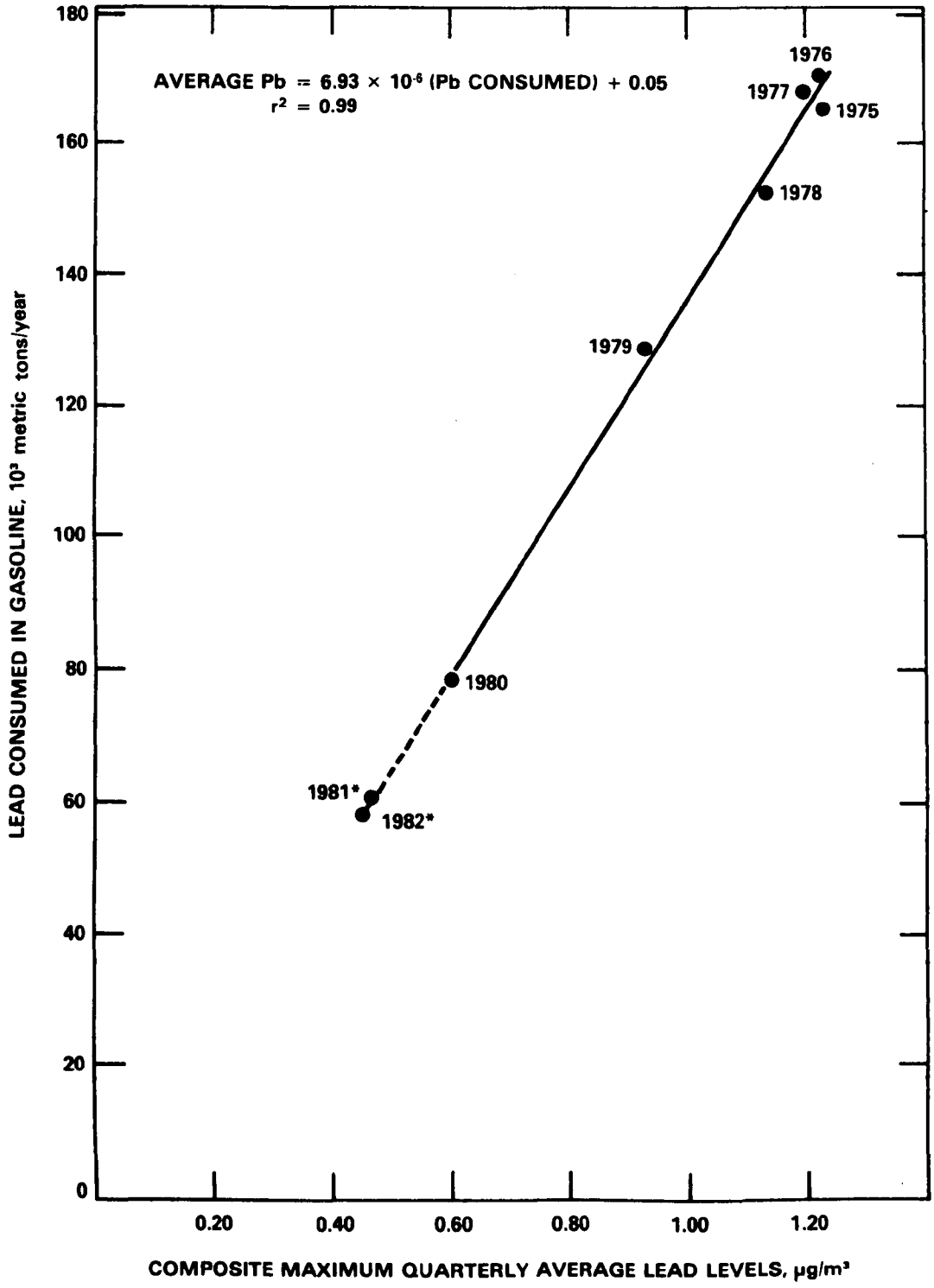

Figure 1-8. Relationship between lead consumed in gasoline and composite maximum quarterly average lead levels, 1975-1980.

***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.

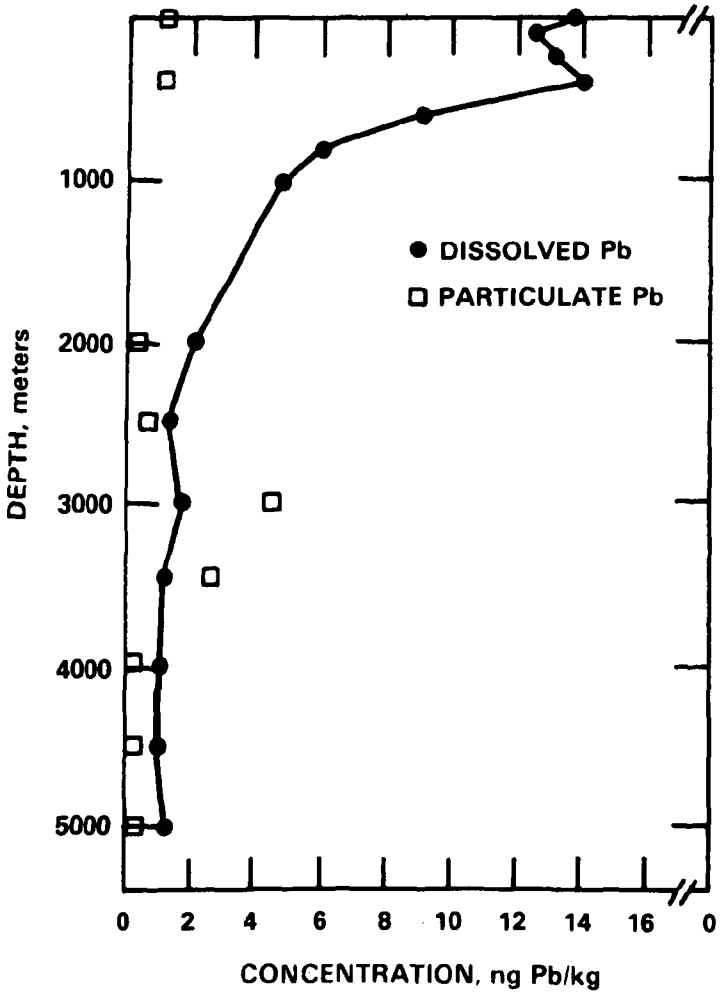

Figure 1-9. Profile of lead concentrations in the central northeast Pacific. Values below 1000 m are an order of magnitude lower than reported by Tatsumoto and Patterson (1963) and Chow and Patterson (1966).

Source: Schaule and Patterson (1980).

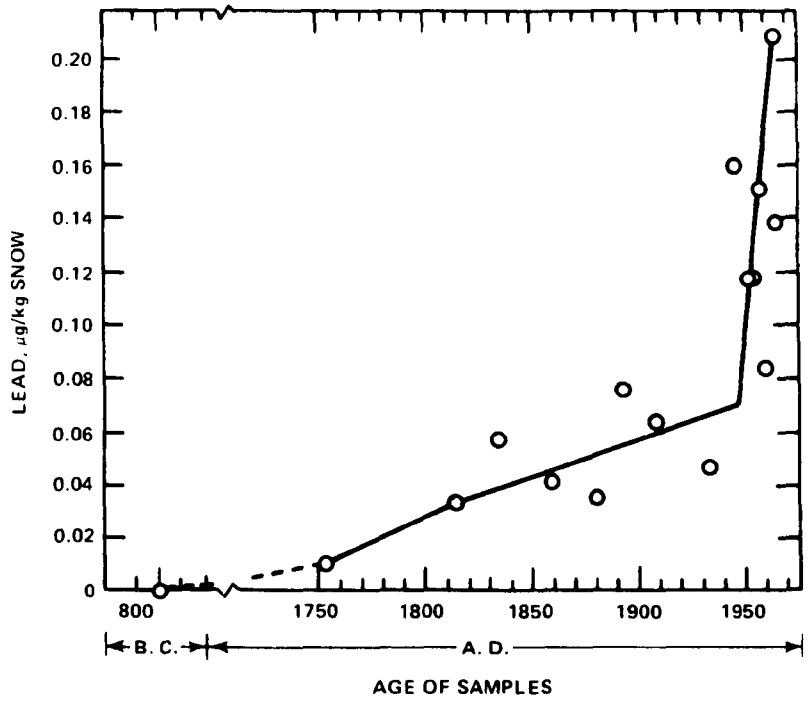

Figure 1-10. Lead concentration profile in snow strata of Northern Greenland.

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.

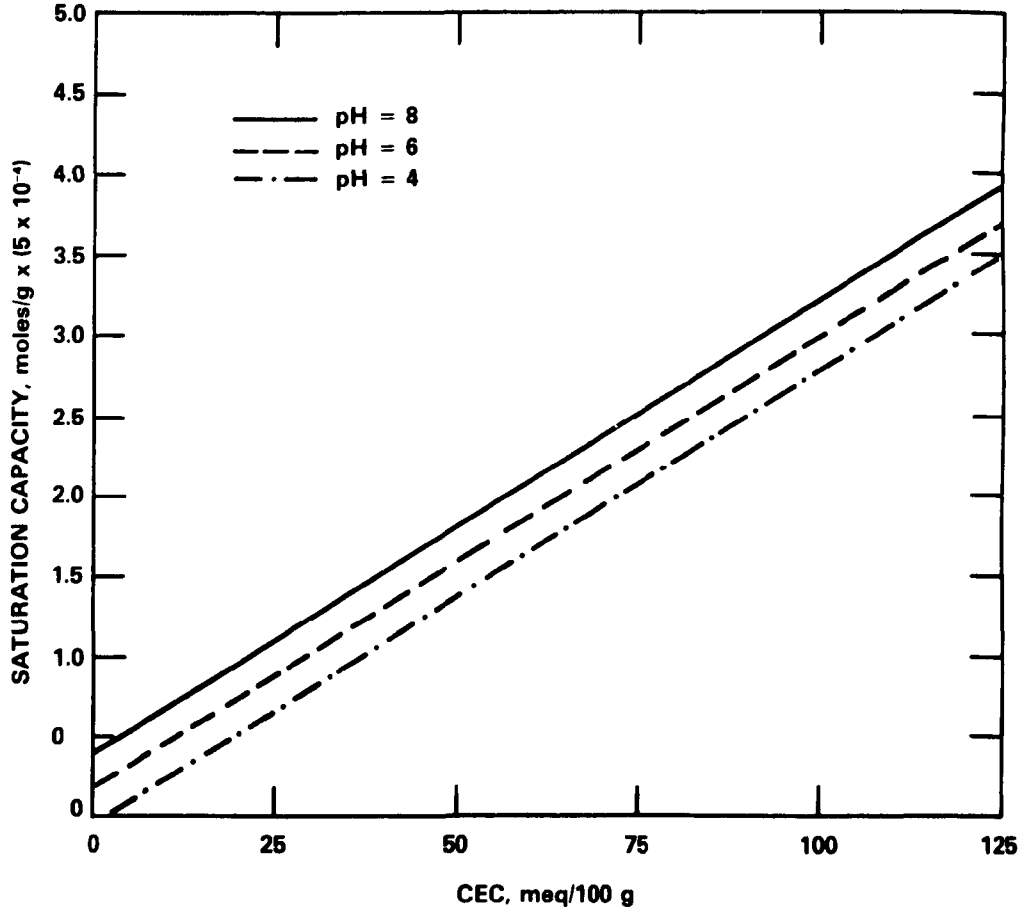

Figure 1-11. Variation of lead saturation capacity with cation exchange capacity in soil at selected pH values.

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·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 µg/g, with a median of 2,400 µg/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

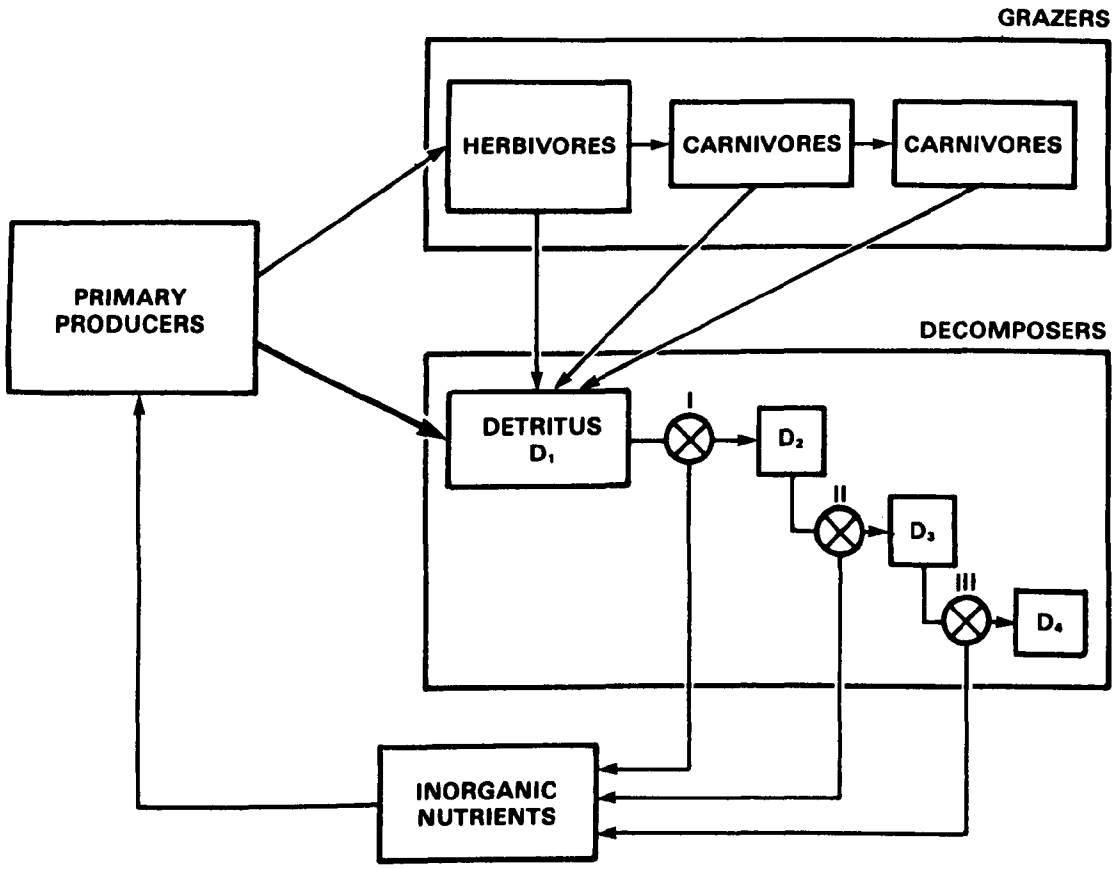

Figure 1-12. This figure depicts cycling processes within the major components of a terrestrial ecosystem, i.e. primary producers, grazers and decomposers. Nutrient and non-nutrient elements are stored in reservoirs within these components. Processes that take place within reservoirs regulate the flow 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 metnod 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 ultraclean 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 noninvasive 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.

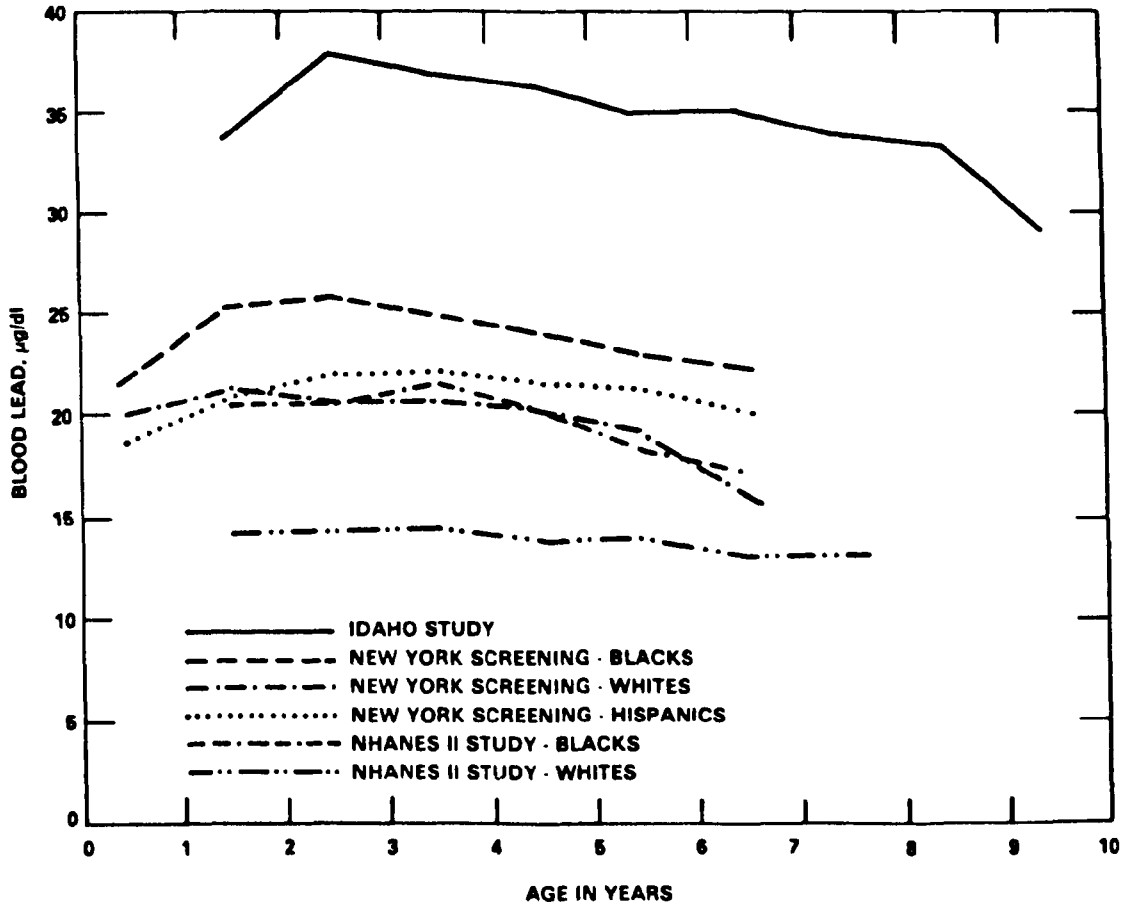

Figure 1-13. Geometric mean blood lead levels by race and age for younger children in the NHANES II study, and the Kellogg/Silver Valley and New York Childhood Screening Studies.

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
	Geometric mean (µg/dl)		
All races			
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.

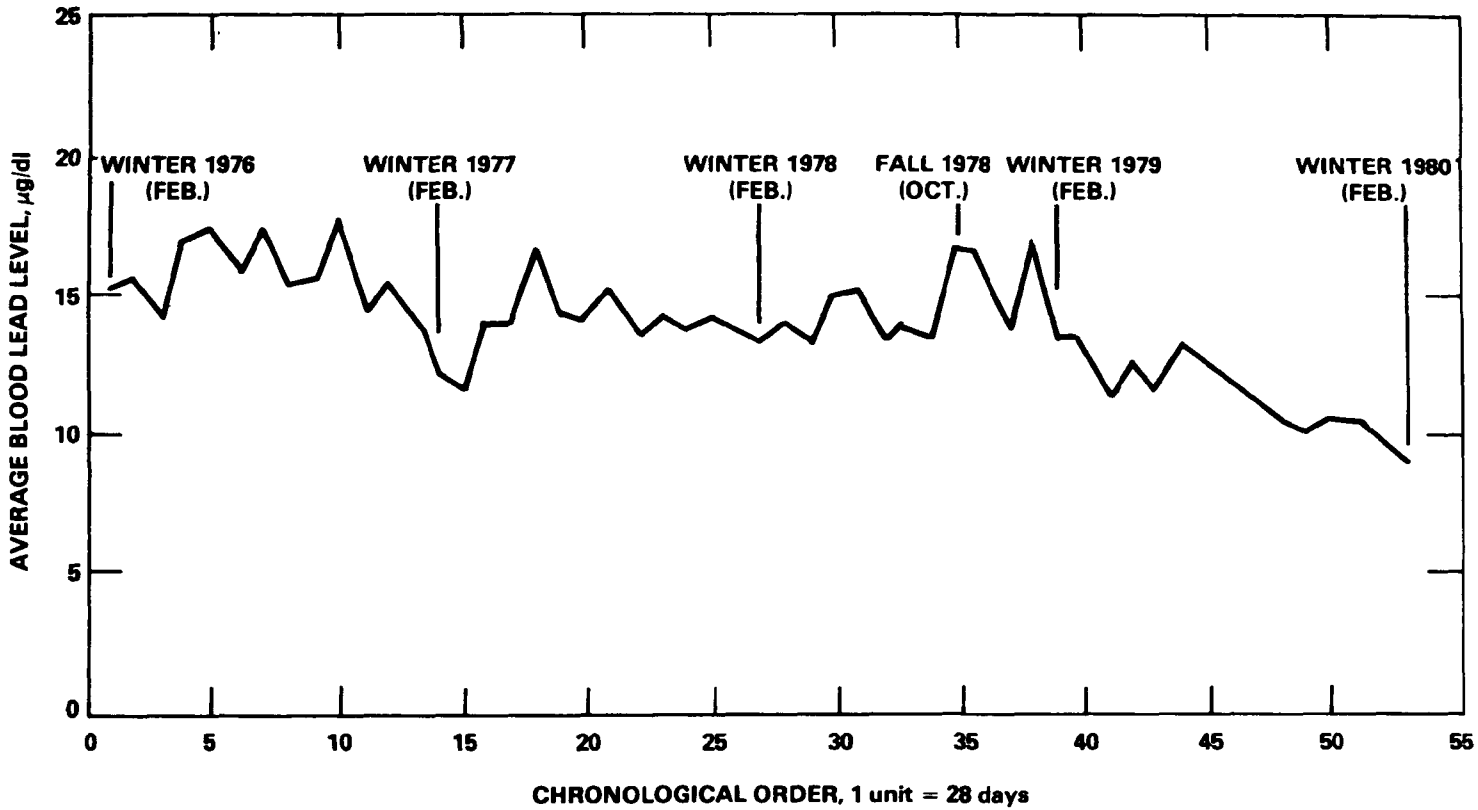

Figure 1-14. Average blood lead levels of U.S. population 6 months—74 years, United States, February 1976—February 1980, based on dates of examination of NHANES II examinees with blood lead determinations.

Source: Annest et al. (1983).

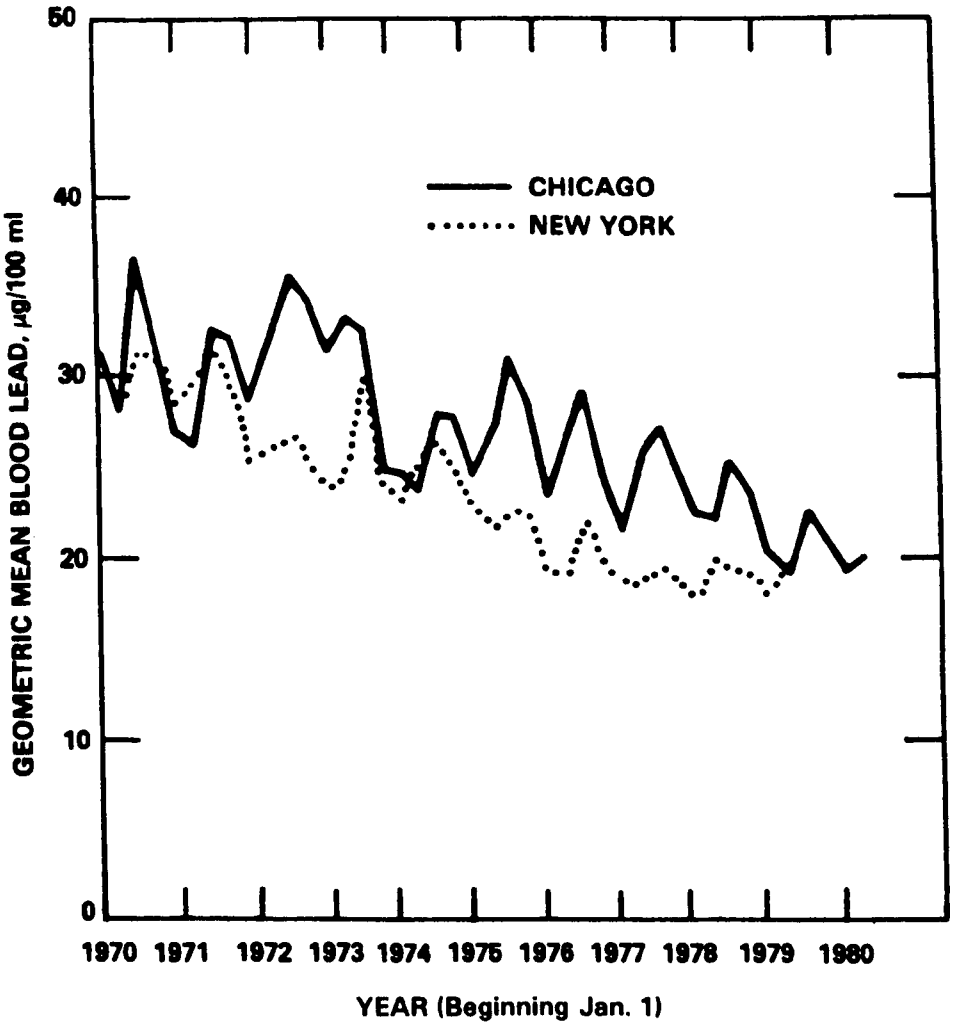

Figure 1-15. Time dependence of blood lead for blacks, aged 24 to 35 months, in New York City and Chicago.

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

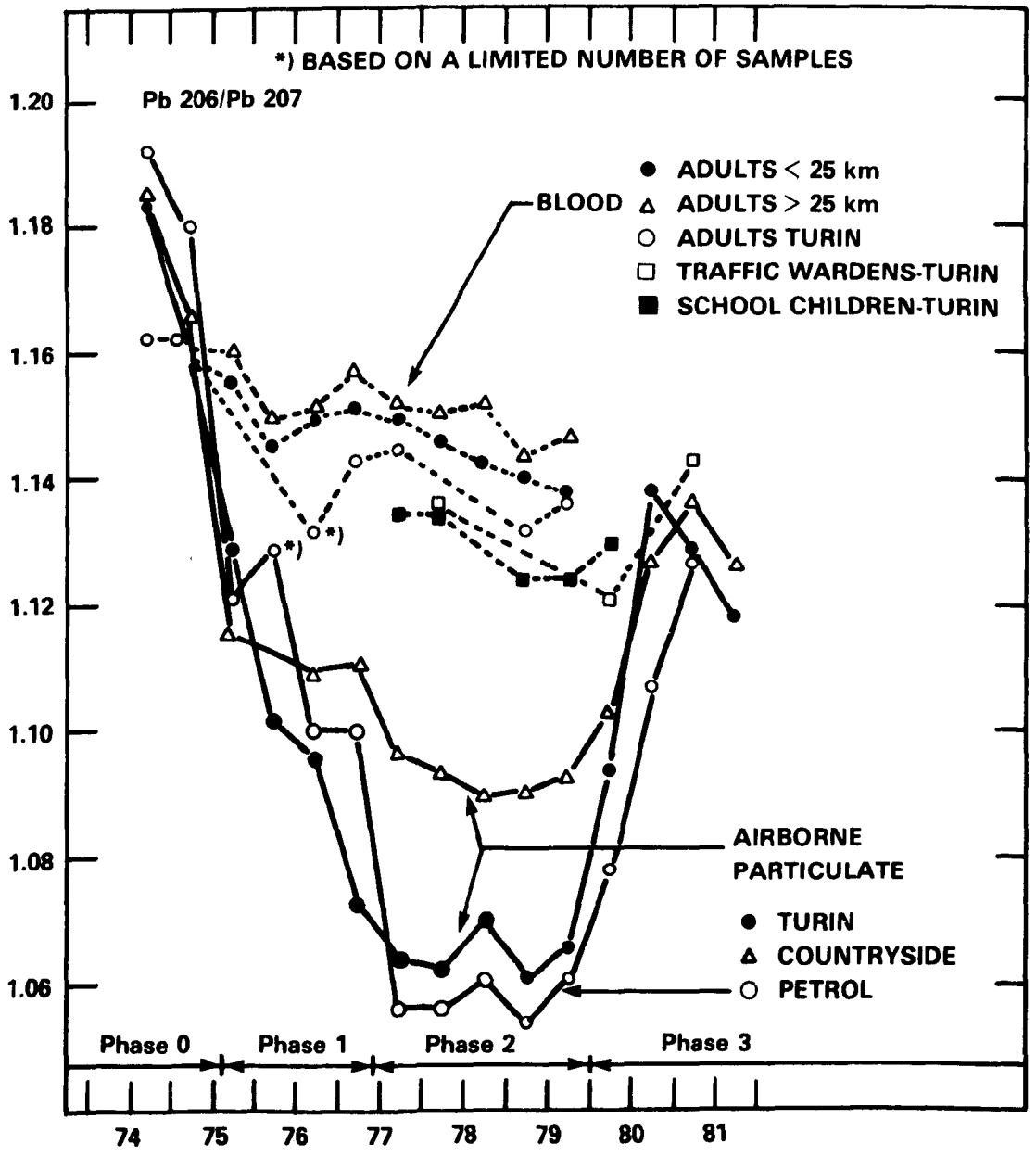

Figure 1-16. Change in Pb-206/Pb-207 ratios in petrol, airborne particulate, and blood from 1974 to 1981.

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

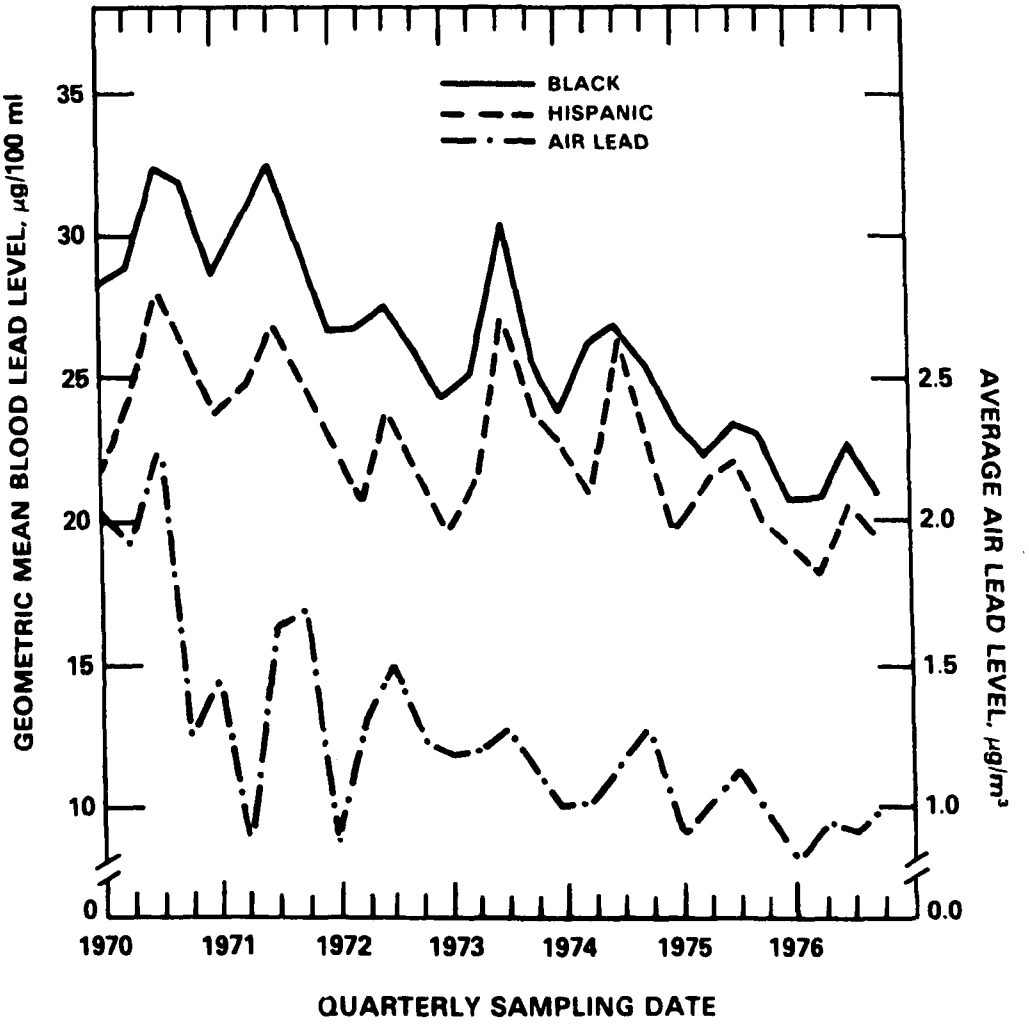

Figure 1-17. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and ambient air lead concentration versus quarterly sampling period, 1970-1976.

Source: Billick et al. (1980).

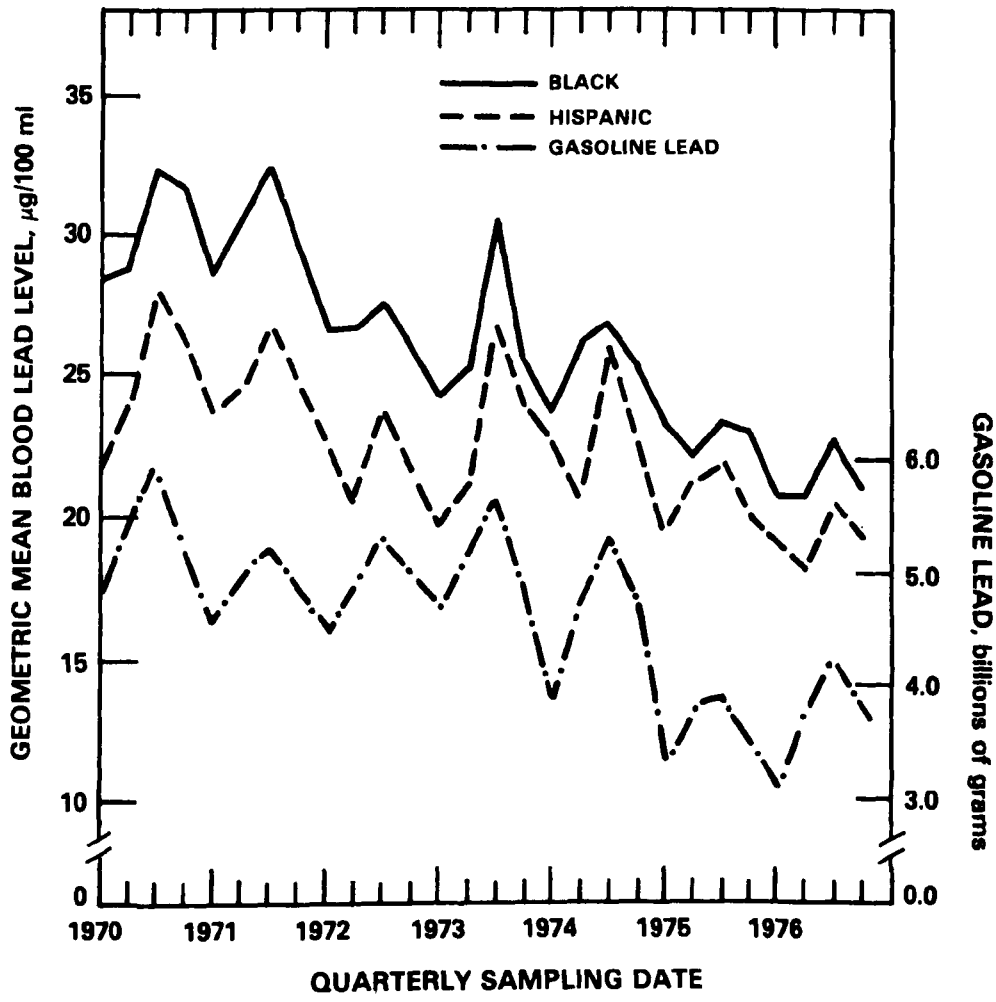

Figure 1-18. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and estimated amount of lead present in gasoline sold in New York, New Jersey, and Connecticut versus quarterly sampling period, 1970-1976.

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 ^{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 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/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.

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 $\leq$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					
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 $\geq$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.

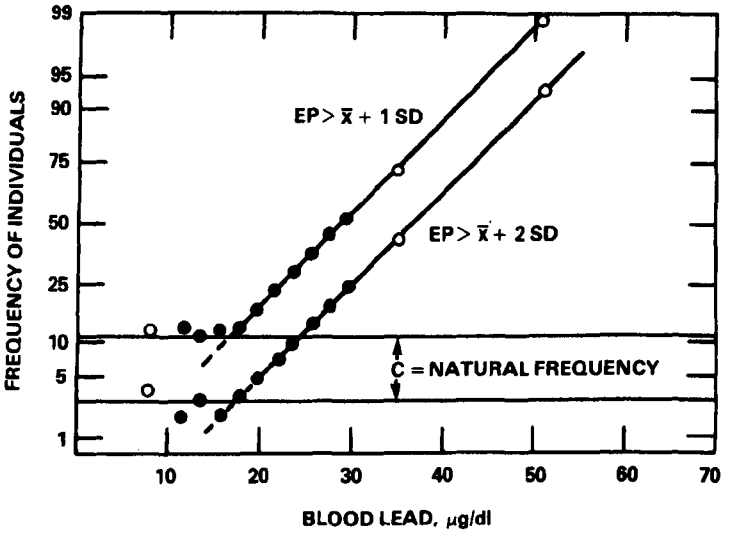

Figure 1-19. Dose-response for elevation of EP as a function of blood lead level using probit analysis. Geometric mean plus 1 S.D. = 33 μg/dl; geometric mean plus 2 S.D. = 53 μg/dl.

Source: Piomelli et al. (1982).

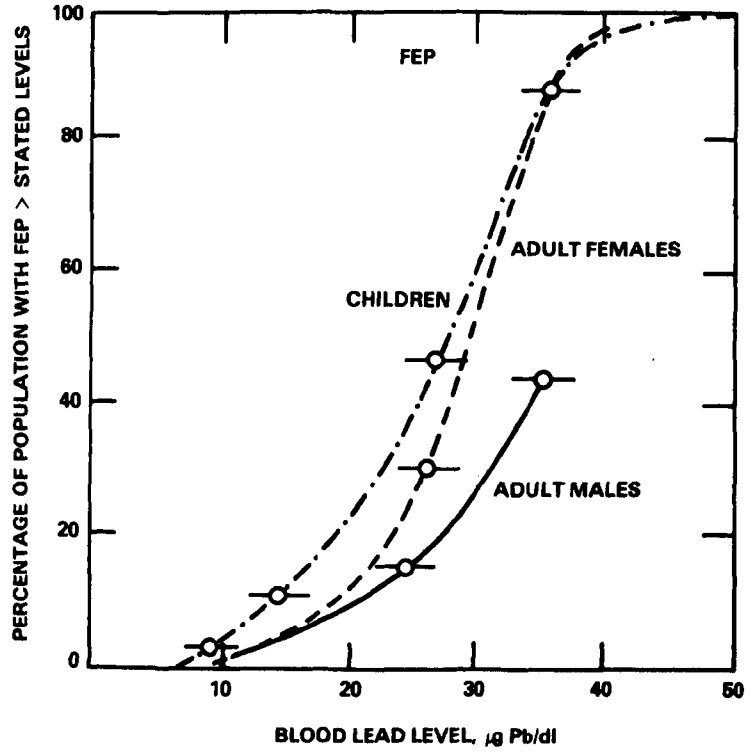

Figure 1-20. Dose-response curve for FEP as a function of blood lead level: in subpopulations.

Source: Roels et al. (1976).

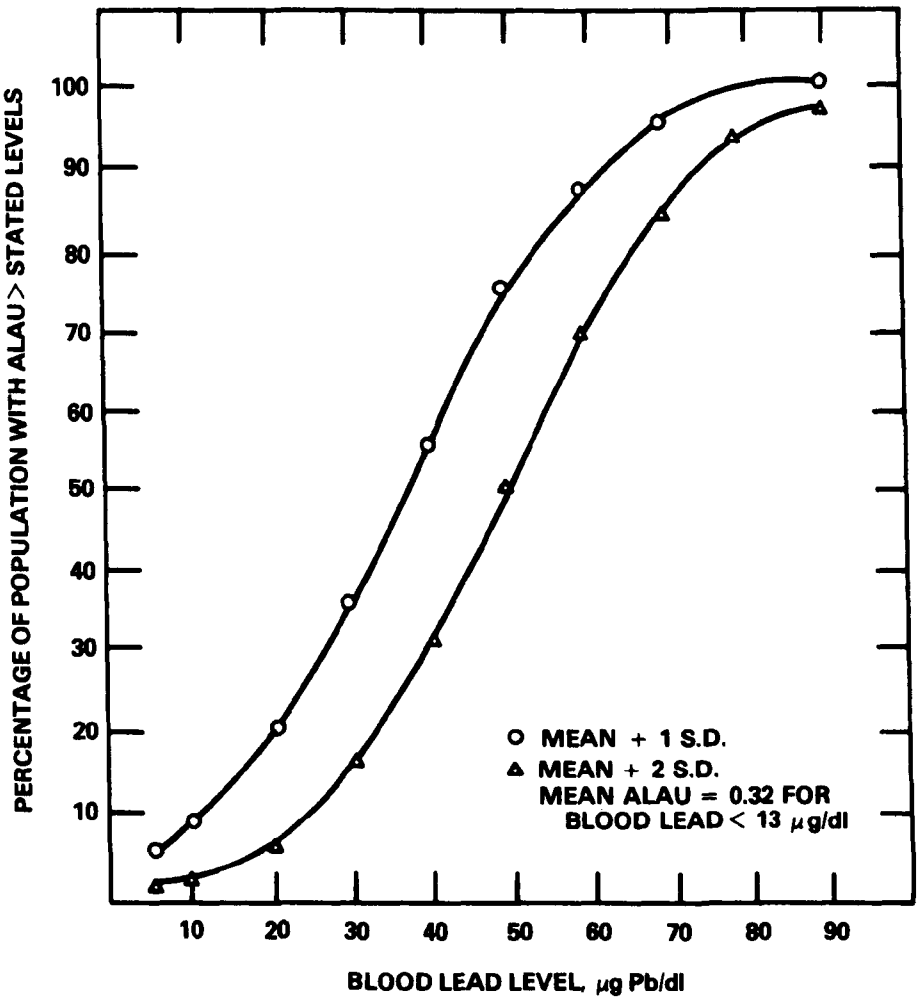

Figure 1-21. EPA calculated dose-response curve for ALA-U.

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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