EPA-600/8-79-003
January 1979

HEALTH ASSESSMENT DOCUMENT FOR CADMIUM

(PREPRINT)

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Environmental Criteria and Assessment Office
Research Triangle Park, North Carolina 27711

EPA-600/8-79-003
January 1979

HEALTH ASSESSMENT DOCUMENT FOR CADMIUM

(PREPRINT)

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Environmental Criteria and Assessment Office
Research Triangle Park, North Carolina 27711

PREFACE

This document deals with the various aspects of cadmium as an Air pollutant in accordance with Section 122(a) of the Clean Air Act as amended in August 1977. Section 122(a) requires that

> "Not later than one year after date of enactment of this section and after notice and opportunity for public hearing, the Administrator shall review all available relevant information and determine whether or not emissions of ... cadmium ... into the ambient air will cause, or contribute to, air pollution which may reasonably be anticipated to endanger public health."

If the Administrator does affirmatively decide that emissions of cadmium do endanger public health,

> "he shall simultaneously with such determination include such substance in the list published under section 108(a)(1) or 122(b)(1)(A) ..., or shall include each category of stationary sources limiting such substance in significant amounts in the list published under section 111(b)(1)(A), or take any combination of such actions."

This decision document is intended to serve as the basis for the Administrator's evaluation of cadmium as an air pollutant. While the preparation of this document has required a comprehensive review of current scientific knowledge regarding airborne cadmium, the references cited do not constitute a complete bibliography.

The Agency acknowledges the contributions of each individual who participated in the development of this document. However, the Environmental Protection Agency accepts full responsibility for the contents herein.

ABSTRACT

The purpose of the present document is to provide a critical assessment of health effects and public health risks associated with environmental exposure to cadmium. In keeping with this objective, major current sources and routes of exposure are identified and discussed as are key health effects associated with cadmium exposure. Furthermore, dose-effect and dose-response relationships are characterized and populations at special risk are delineated. Lastly, the potential impact of current and likely future exposure patterns on the health of the American public is analyzed.

Cadmium is naturally present in trace amounts in most environmental media including soil, water, air, and food. Substantial additional amounts of the element are added to each of these media as a consequence of man's activities. Included among major anthropogenic sources are: (1) smelting and mining operations; (2) electroplating and certain other manufacturing operations; and (3) waste disposal operations, e.g., municipal incineration and land application of solid waste materials. Man is exposed to cadmium dissipated by each of these sources either directly through emissions into ambient air or water or indirectly via secondary deposition of the element on soils and subsequent uptake into the human food chain.

Food is presently the single largest environmental source of cadmium exposure for most humans. Current estimates of average daily dietary cadmium intake for Americans vary from 10 to 50 μg/day. Cigarette smoking (one to three packs per day) can significantly increase cadmium intake in amounts equal to or exceeding that obtained from food. General ambient

air and drinking water contribute only small increments in cadmium uptake beyond that of food or cigarette smoking. Exceptions to this may exist in areas surrounding certain point sources that emit high levels of cadmium.

Two major types of adverse health effects of cadmium exposure can be distinguished--acute and chronic. Acute cadmium toxicity usually results from inhalation of cadmium at high-dose levels encountered in occupational settings. In cases of nonlethal inhalation exposure, chronic respiratory effects (pneumonitis) are of primary concern. In contrast, long-term, lower-level exposures to cadmium via air or other media, e.g., food, are of most concern because consequent accumulations of cadmium in the kidney induce associated renal tubular dysfunction as the "critical effect" of chronic cadmium exposure.

The most accurate index of the effective internal cadmium dose necessary to induce renal dysfunction is the concentration of the metal in the renal cortex. The most common currently accepted value for the "critical concentration" of cadmium in the kidney is 200 μg/g wet weight of renal cortex. Estimates of external exposure levels sufficient to cause the critical renal cortex concentration to be reached vary considerably. For example, estimates of requisite ingestion levels derived from various metabolic modeling approaches range from 200 to 480 μg/day, and levels near the lower end of the range (200 to 250 μg/day) are presently being seen as the best estimates of "threshold" dietary intake levels typically needed to result in the critical renal cortex concentration being reached over a 50-year exposure period. Other approaches utilizing actual measures of dietary cadmium exposures and associated prevalence of renal dysfunction, however,

suggest that wide variability may exist across human populations in regard to ingestion levels necessary to induce the critical effect; such studies suggest that 1 percent, 2.5 percent, and 5 percent of the American population, for example, would be affected at 60, 80, and 100 μg cadmium intake per day, respectively, assuming a 50-year period.

Due to the accumulative nature of cadmium retention in the kidney, older members (i.e., over 40 to 50 years of age) of exposed populations typically have both the highest renal cortex concentrations of the metal and the highest prevalence of cadmium-induced renal dysfunction. Thus, older members of the United States population would be expected to be most immediately at risk for future increments in cadmium exposure. Also, due to increased absorption of cadmium being associated with certain nutritional deficiencies, e.g., insufficient levels of dietary iron, zinc, or cadmium, older members of the population with such nutritional deficits are likely to be at even greater risk. Since everyone ages and is therefore subject to long-term renal cadmium accumulation, the entire United States population should be considered at potential risk for cadmium-induced renal dysfunction. Also, since smokers are exposed to and retain significantly higher levels of cadmium than non-smokers, they are clearly at greater risk for cadmium-induced adverse health effects.

SCIENCE ADVISORY BOARD

SUBCOMMITTEE ON CADMIUM AS A POSSIBLE HAZARDOUS AIR POLLUTANT

The substance of this document was reviewed by the Environmental Protection Agency's Science Advisory Board Subcommittee on Cadmium as a Possible Hazardous Air Pollutant, in public session. The subcommittee was comprised of the following individuals:

Chairman:

Dr. Ruth R. Levine, Chairman, Graduate Division of Medicine and Dentistry, Boston University Medical School, Boston, Massachusetts 02215

Members:

Dr. Ursula M. Cowgill, Professor of Biology, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Dr. Robert A. Duce, Professor, Graduate School of Oceanography, University of Rhode Island, West Kingston, Rhode Island 02892

Dr. Thomas J. Haley, Assistant to the Director, National Center ofr Toxicological Research, Jefferson, Arkansas 72079

Dr. Harold M. Peck, Senior Director, Department of Safety Assessment, Merck Institute of Therapeutic Research, Merck, Sharp, and Dohme, West Point, Pennsylvania 19486

Ms. Anne Wolven, Consultant, Atlanta, Georgia 30328

Staff Officer:

Dr. Joel L. Fisher, Science Advisory Board, U.S. Environmental Protection Agency, 401 M Street S.W., Washington, D.C. 20460

CONTRIBUTORS AND REVIEWERS

Authors

Dr. Lester D. Grant, Associate Professor, Departments of Psychiatry and Anatomy, University of North Carolina, School of Medicine, Chapel Hill, North Carolina 27514

Dr. Paul Mushak, Associate Professor of Pathology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina 27514

Dr. Annemarie Crocetti, Adjunct Associate Professor of Preventive and Community Medicine, New York Medical College, New York, New York 10029

Mr. Warren Galke, Environmental Criteria and Assessment Office, Environmental Research Center, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Consultants

Dr. George M. Cherian, Assistant Professor, Department of Pathology, University of Western Ontario, London, Ontario, Canada

Dr. Gunnar Nordberg, Institute of Community Health and Environmental Medicine, Odense University, Odense, Denmark.

Dr. H. M. Perry, Jr., Washington University School of Medicine, St. Louis, Missouri

Dr. Magnus Piscator, Department of Environmental Hygiene, The Karolinska Institute, Stockholm, Sweden

Dr. Samuel Shibko, Division of Toxicology, Food and Drug Administration, Washington, D.C.

EPA Review Committee

Dr. J. H. B. Garner, Chairman, Environmental Criteria and Assessment Office, Environmental Research Center, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Dr. Donald E. Gardner, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Dr. Vic Hasselblad, Health Effects Research Laboratory, Environmental Research Center, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Dr. Robert J. M. Horton, Health Effects Research Laboratory, Environmental Research Center, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Dr. Joellen Huisingh, Health Effects Research Laboratory, Environmental Research Center, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Mr. Richard Johnson, Strategies and Air Standards Division, Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Technical and Editorial Assistance

Ms. Gayla Benignus, Private Consultant, Chapel Hill, North Carolina 27514

Mr. Douglas B. Fennell, Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Ms. Evelynne Rash, Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Ms. Frances V. P. Duffield, Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

CONTENTS

	Page
LIST OF FIGURES	xiii
LIST OF TABLES	xiv
ABSTRACT	iv
1. SUMMARY AND CONCLUSIONS	1-1
1.1 INTRODUCTION	1-1
1.2 HEALTH ASPECTS OF CADMIUM IN MAN AND ANIMALS	1-4
1.2.1 Metabolism of Cadmium in Man and Experimental Animals	1-4
1.2.2 Biological and Adverse Health Effects in Man and Animals	1-7
1.3 EFFECTS OF CADMIUM ON HUMAN POPULATIONS	1-13
1.4 HUMAN HEALTH RISK ASSESSMENT OF CADMIUM	1-18
1.4.1 Introduction	1-18
1.4.2 Sources and Routes of Exposure	1-18
1.4.3 Human Population Responses to Cadmium in Human Risk Assessment	1-21
1.4.4 Overall Conclusions	1-33
2. BIOLOGICAL SIGNIFICANCE AND ADVERSE HEALTH EFFECTS OF CADMIUM	2-1
2.1 INTRODUCTION	2-1
2.2 METABOLISM OF CADMIUM	2-2
2.2.1 Sources of Exposure	2-2
2.2.2 Inhalation	2-3
2.2.3 Gastrointestinal Absorption	2-4
2.2.4 Other Absorption Routes	2-4
2.2.5 Transport and Deposition	2-4
2.2.6 Excretion	2-6
2.3 SUB-CELLULAR AND CELLULAR ASPECTS OF CADMIUM TOXICITY	2-7
2.3.1 General Sub-Cellular Effects	2-7
2.3.2 Metallothionein	2-22
2.4 RESPIRATORY EFFECTS OF CADMIUM	2-27
2.4.1 Effects on Humans	2-27
2.4.2 Animal Studies	2-29
2.5 RENAL EFFECTS OF CADMIUM	2-32
2.5.1 Animal Studies	2-33
2.5.2 Human Studies	2-37
2.6 THE CARDIOVASCULAR SYSTEM	2-41
2.6.1 Animal Studies	2-41
2.6.2 Human Hypertension	2-44
2.7 EFFECTS OF CADMIUM ON REPRODUCTION AND DEVELOPMENT	2-44
2.7.1 Testicular Effects	2-44
2.7.2 Ovarian Effects	2-54
2.7.3 Embryotoxic and Teratogenic Effects	2-55

Page

2.8 ENDOCRINE EFFECTS OF CADMIUM..... 2-70
2.8.1 Gonadal Effects..... 2-71
2.8.2 Pancreatic Effects..... 2-71
2.8.3 Adrenal Effects..... 2-73
2.8.4 Thyroid Effects..... 2-75
2.8.5 Pituitary Effects..... 2-76
2.9 EFFECTS OF CADMIUM ON BONE AND MINERAL METABOLISM..... 2-76
2.9.1 Animal Studies..... 2-77
2.9.2 Human Aspects..... 2-78
2.10 HEPATIC EFFECTS OF CADMIUM..... 2-78
2.10.1 Animal Studies..... 2-79
2.10.2 Human Aspects..... 2-80
2.11 NEUROLOGICAL EFFECTS OF CADMIUM..... 2-81
2.12 GASTROINTESTINAL EFFECTS OF CADMIUM..... 2-85
2.13 HEMATOLOGICAL EFFECTS OF CADMIUM..... 2-86
2.14 IMMUNOSUPPRESSIVE EFFECTS OF CADMIUM..... 2-88
2.15 MUTAGENIC AND CARCINOGENIC EFFECTS OF CADMIUM..... 2-90
2.15.1 Mutagenic Effects of Cadmium..... 2-91
2.15.2 Tumorigenic Cadmium Effects in Animals..... 2-94
2.15.3 Human Carcinogenesis Studies..... 2-100
2.16 INTERACTIONS OF CADMIUM WITH OTHER METABOLIC FACTORS..... 2-103
2.16.1 Zinc..... 2-103
2.16.2 Selenium..... 2-104
2.16.3 Calcium..... 2-107
2.16.4 Iron..... 2-107
2.16.5 Cooper..... 2-108
2.17 REFERENCES FOR CHAPTER 2..... 2-110

3. HUMAN EPIDEMIOLOGY..... 3-1
3.1 INTRODUCTION..... 3-1
3.2 CADMIUM IN HUMAN POPULATIONS..... 3-1
3.2.1 Sources of Variations in Human Blood Cadmium Levels..... 3-2
3.2.2 Sources of Variation in Human Urine Cadmium Levels..... 3-14
3.2.3 Sources of Cadmium Variation in Human Hair..... 3-20
3.3 RESULTS OF AUTOPSY STUDIES..... 3-22
3.4 EPIDEMIOLOGICAL STUDIES OF CADMIUM EXPOSURE IN JAPAN..... 3-29
3.4.1 Itai-Itai Disease..... 3-30
3.4.2 Epidemiological Studies of Other Cadmium-Polluted Areas in Japan..... 3-33
3.5 EPIDEMIOLOGY OF CADMIUM, HYPERTENSION, AND CARDIO-VASCULAR DISEASES..... 3-35
3.6 EPIDEMIOLOGICAL STUDIES OF THE RESPIRATORY TRACT..... 3-38
3.7 CADMIUM AND CANCER..... 3-39
3.8 EPIDEMIOLOGICAL STUDIES RELATING TO CHROMOSOMAL ABNORMALITIES..... 3-43

Page

3.9 EPIDEMIOLOGICAL STUDIES OF OCCUPATIONAL EXPOSURE IN JAPAN..... 3-44
3.10 REFERENCES FOR CHAPTER 3..... 3-45

4. HUMAN HEALTH RISK ASSESSMENT OF CADMIUM..... 4-1
4.1 INTRODUCTION AND DEFINITION OF TERMS..... 4-1
4.2 EXPOSURE ASPECTS..... 4-4
4.2.1 Ambient-Air Levels of Cadmium..... 4-5
4.2.2 Drinking Water..... 4-13
4.2.3 Soils..... 4-15
4.2.4 Food..... 4-30
4.2.5 Other Sources..... 4-46
4.3 HEALTH EFFECTS SUMMARY..... 4-48
4.4 DOSE-EFFECT AND DOSE-RESPONSE RELATIONSHIPS OF CADMIUM IN HUMANS..... 4-52
4.4.1 Dose Aspects..... 4-52
4.4.2 Dose-Effect/Dose-Response Aspects..... 4-53
4.5 POPULATIONS AT RISK TO EFFECTS OF CADMIUM..... 4-66
4.6 UNITED STATES POPULATION GROUPS IN RELATION TO PROBABLE CADMIUM EXPOSURES..... 4-79
4.7 REFERENCES FOR CHAPTER 4..... 4-89

FIGURES

Number		Page
3-1.	Cadmium concentration in urine of Tokyo inhabitants plotted by age shows age-dependent relationship.....	3-18
3-2.	Geometric and arithmetic means of cadmium concentration in kidney cortex are shown for each decade of life.....	3-26
3-3.	Cadmium in whole kidney tissues and its relationship to age.....	3-29
4-1.	Diagrammatic representation of multi-media routes by which cadmium exposure of man can occur after dissipation of the element into the environment by anthropogenic activities.....	4-6
4-2.	Trends in 50th percentile of annual averages for cadmium associated with metal industry sources at urban sites.....	4-11
4-3.	Contribution of food groups to cadmium intake.....	4-36
4-4.	Effects of soil pH on cadmium uptake by vegetables.....	4-41
4-5.	Calculated (lines) and observed (symbols) dose-response relationships for cadmium-induced increase (>97.5) percentile of reference group) of urinary β_2-microglobulin excretion. (From Kjellström, 1977).....	4-62
4-6.	Regions used in cadmium analysis.....	4-85

TABLES

Number		Page
1-1.	Cadmium exposure required for reaching a kidney cortex concentration of 200 μg Cd/g using different alternatives for biological half-time in kidney cortex and exposure time	1-23
1-2.	Media contributions to normal retention of cadmium	1-24
1-3.	Food exposure: calculated intakes that may give a certain response rate at age 50	1-26
1-4.	Estimated relative contribution of dietary intake, cigarette smoking, and ambient air cadmium levels to total daily cadmium retention from all sources	1-31
2-1.	Sub-cellular and cellular cadmium toxicity in experimental animals	2-9
2-2.	Species variations in susceptibility to cadmium-induced testicular necrosis	2-47
2-3.	Cadmium in placentas and fetuses	2-65
2-4.	Placental to maternal blood concentration ratios	2-66
2-5.	Placental to fetal cadmium concentration ratios	2-67
2-6.	Effects of maternal dietary cadmium, given during gestation, on body weights and body trace metals of neonates	2-69
2-7.	Summary of mutagenicity test results	2-92
2-8.	Studies on cadmium tumorigenesis in experimental animals	2-96
2-9.	Summary of results of human epidemiologic studies of cancer effects associated with occupational exposures to cadmium	2-102
3-1.	"Normal" blood cadmium levels	3-7
3-2.	"Normal" urine cadmium levels	3-16
3-3.	Urine cadmium levels for "normal" males in Dallas, Texas, determined by atomic absorption	3-19
3-4.	Cadmium in human liver	3-24
3-5.	Cadmium concentration in human renal cortex by age: means and 99% level of significance	3-25
3-6.	Age group means and standard deviations for tissue cadmium	3-25
3-7.	Mean cadmium values related to place of residence	3-28
4-1.	Annual average urban atmospheric cadmium concentrations reported by National Air Surveillance Networks, 1970-1974	4-8
4-2.	Cadmium in soils	4-16
4-3.	Concentrations of cadmium in urban and suburban soils - 1972	4-17
4-4.	Amounts of municipal sewage sludge of varying cadmium content annually produced by major U.S. cities and applied to agricultural land by landspreading	4-20

Number		Page
4-5.	Cadmium content in different food categories in the U.S.A.	4-32
4-6.	Cadmium content of selected adult foods	4-34
4-7.	Food groups by mean cadmium content and their contribution to daily cadmium intake	4-35
4-8.	Cadmium intake of teen-age males by food class	4-37
4-9.	Cadmium content of several crops and tissues as a function of cadmium loading of soil	4-40
4-10.	Cadmium content of soils and crops grown on acid and limed sludged sites	4-42
4-11.	Media contributions to normal retention of cadmium	4-47
4-12.	Cadmium exposure required for reaching a kidney cortex concentration of 200 μg Cd/g using different alternatives for biological half-time in kidney cortex and exposure time	4-57
4-13.	Food exposure: calculated intakes that may give a certain response rate at age 50	4-64
4-14.	Prevalence of tubular proteinuria and suspected patients among adults more than 50 years of age in relation to village average rice cadmium concentrations	4-65
4-15.	Prevalence of tubular proteinuria in relation to age and village average rice cadmium concentation	4-67
4-16.	Relative contribution of cigarette smoking to total daily cadmium retention	4-47
4-17.	Estimated relative contribution of dietary intake, cigarette smoking, and ambient air cadmium levels to total daily cadmium retention from all sources	4-73
4-18.	Percentage of critical daily cadmium retention level yielding renal dysfunction achieved by smokers at two exposures times and two dietary levels	4-74
4-19.	Percentage of critical daily cadmium retention level yielding renal dysfunction achieved by smokers as a function of ambient air cadmium levels	4-75
4-20.	Average exposure and number of people exposed to annual cadmium levels greater than 0.1 ng/m^3 by specified source types	4-81
4-21.	Comparison of cadmium exposures among sources	4-82
4-22.	Population exposed to cadmium concentrations	4-83
4-23.	Regional breakdown on population exposed to cadmium concentrations greater than 0.1 ng/m^3 from selected stationary sources	4-86
4-24.	Number of births by race and size of population	4-87

1. SUMMARY AND CONCLUSIONS

1.1 INTRODUCTION

The purpose of the present document is to evaluate the toxic effects of cadmium in man and animals and to assess the potential risk to human health associated with environmental exposure to that element. This chapter summarizes the main issues addressed in the document, the most important evidence bearing on these issues, and major conclusions based on the evidence discussed.

Among the issues addressed in the document are the following points of primary concern:

(1) Can demonstrable adverse human health effects presently be associated with exposure to cadmium; and are such health effects reversible or irreversible? Of particular interest is whether cadmium induces sufficiently deleterious effects on human health or welfare to warrant its classification as a "hazardous air pollutant?"

(2) What are the major sources of cadmium exposure in human populations, especially among Americans, and what are the most important routes of exposure that currently exist? Can the relative contributions of different sources and routes of exposure to uptake and retention of the element in the general population be estimated? If so, with what degree of confidence? Related to this is the issue of sensitivity and accuracy of existing measurement methodology for determining levels of cadmium in tissue matrices and nonbiological materials.

(3) Based on known exposure information and taking into account other interacting factors, can particular human populations be identified

as being at special risk for adverse health effects due to cadmium exposure? If so, under what circumstances and in what numbers are the members of those populations expected to be at unacceptable risk?

No exhaustive compilation of the extensive currently available literature on the toxicity of cadmium is provided. Rather, a much more selective review and evaluation of the pertinent literature related to the above points of concern is presented. The evaluation of toxic effects of cadmium in animals and man is based upon (1) studies of cadmium intoxication in experimental animal models and (2) human epidemiological and clinical research. In addition, in assessing the potential risk to human health associated with exposure to cadmium, major sources of cadmium exposure are identified, and their present relative contributions to human intake and retention of the metal are estimated, dose-effect and dose-response relationships for the occurrence of certain crucial health effects are defined, and the levels of cadmium retention at which such "critical effects" of acute and chronic exposure occur are indicated. Estimations are also made of cadmium exposure levels necessary to achieve sufficient retention of the metal for induction of the critical effects of acute and chronic exposure. Lastly, populations at special risk for exhibiting the critical adverse health effects are delineated according to particular factors that place them at greater risk than others, and projections are made regarding numbers of such people likely to be adversely affected by excessive environmental exposure to cadmium.

Several points of considerable concern from a public health standpoint emerge from the present analysis. One is that cadmium appears to be

somewhat unique among the elements exerting toxic effects on man and other living organisms in that: (1) its half-time in the body is unusually long, sufficiently long that active accumulation of the element occurs over most of the lifetime of man; (2) its accumulation does not include major deposition as an "inert" fraction in bone, as is the case with lead, but rather it is lodged in soft tissue, chiefly the kidney; and (3) its consequent adverse health effects, especially where clinically manifest, appear to be essentially irreversible.

Another matter of concern is that large numbers of the general American population appear to be regularly exposed to cadmium from many sources, but mainly food, and that retention levels are such that only a relatively small margin of safety exists for some individuals. Thus, any additional cadmium accumulation over a long period of time may approach levels sufficient to cause adverse health effects in significant segments of the United States population. Of particular concern in that regard is the fact that cigarette smoking contributes very significant amounts of cadmium to body levels, at times equivalent to or more than that derived from food, thus placing millions of existing and future smokers at special risk.

Also of much concern are projections that can reasonably be made regarding certain developments that could potentially increase hazards from cadmium exposure in the future, if adequate safeguards or regulatory controls are not implemented. More specifically, although present exposures to existing levels of atmospheric cadmium generally do not now appear to pose much risk to most Americans, two developments could substantially increase ambient air levels of cadmium, i.e.: (1) expanded municipal incineration

of high-cadmium content sewage sludge or other waste materials; and (2) expanded fossil fuel use, especially anticipated large increases in coal burning at coal-fired power plants. Increased ambient air cadmium levels from the above sources, if not adequately controlled, would not only pose greater health risks via increased cadmium exposure through direct inhalation, but would also be expected to increase levels of cadmium ingested in food and water via secondary deposition of airborne particles on agricultural land and water. Other developments which could more directly impact on amounts of cadmium introduced into the human food chain are: (1) expanded use of cadmium-contaminated phosphate fertilizers on agricultural land; and (2) increased landspreading of cadmium-containing sewage sludge or other waste materials on agricultural land used for growing food crops.

1.2 HEALTH ASPECTS OF CADMIUM IN MAN AND ANIMALS

A variety of biological and adverse health effects have been documented in experimental animals and man under conditions of acute and chronic cadmium exposure. It should be noted that, as far as can best be determined, cadmium plays no beneficial or essential role in the health of man or animals. In view of this, demonstrated biological and adverse health effects of this particular element must be considered in the absence of any health benefit--health cost balance.

1.2.1 Metabolism of Cadmium in Man and Experimental Animals

Cadmium, like other multi-media environmental contaminants, may be introduced into the target organism from a number of sources, including air, food, and water. The relative amount of cadmium inhaled and absorbed via the pulmonary tract depends on the physiochemical character of the form of airborne cadmium as well as subsequent fate of the cadmium deposited in the respiratory tract.

More specifically, the extent of deposition in the pulmonary tract is a function of particle size and solubility. Deposition in lung is about 50 percent for particles of 0.1 micrometer mass diameter (MMD) down to 10 percent for particles of 5.0 micrometers MMD. Systemic absorption of the amount deposited in the respiratory tract of man is estimated to be from 20 to 25 percent of the deposited fraction. The amount of cadmium absorbed from inhalation of cigarette smoke, however, may be significantly higher.

Since human populations generally acquire most of their cadmium from dietary intake, gastrointestinal absorption is the major route of entry of cadmium into man. About 6 percent of the cadmium entering the gastrointestinal tract is absorbed; based on clinical and epidemiological observations, however, nutritional deficiencies such as low calcium and iron can markedly increase this figure.

Blood is the vehicle for transport of cadmium absorbed via inhalation or ingestion. Cadmium is then taken up from the blood into the liver, where incorporation into metallothionein occurs, followed by release into blood and deposition of cadmium-thionein in the kidney. In populations with minimal exposure to cadmium, about half of the organ distribution of cadmium is in the liver and kidneys, with the kidneys accounting for about one-third of the total body burden. Other organs accumulating cadmium include the testes, lungs, pancreas, spleen, and various endocrine organs. In contrast, cadmium concentration in bone, brain, and muscle tissue is very low.

The half-time of cadmium in the body, a measure of its retention or accumulation, has been calculated to be 18 to 38 years. Whereas, little cadmium is typically found in man at birth, a steady accumulation of the element occurs up to about 50 years of age, with a very large portion of the

accumulating cadmium being retained in soft tissue such as the kidney. Beyond 50 years of age, the levels of renal cadmium usually reach an asymptotic level and remain essentially constant or dec[illegible]re

Cadmium is excreted mainly via the urinary and gastrointestinal tracts; daily urinary excretion is less than 1 μg in the non-smoking population. Cadmium exposure from whatever source tends to increase the daily urinary output of the element. Biliary excretion occurs in animals but has not yet been demonstrated to be significant in man.

The transport and toxicity of cadmium are intimately associated with an inducible metal-binding protein, metallothionein, which binds cadmium, zinc, and certain other divalent metal ions. On absorption, cadmium is transported via blood to the liver where it is incorporated into metallothionein. The protein-bound cadmium is then released back into the blood and undergoes deposition in the kidney and other soft tissues. The binding of cadmium by metallothionein and the deposition of the complex in kidney and other soft tissue apparently accounts for its very long half-time in the body, and a number of studies show that the relative toxicity of cadmium incorporated into metallothionein is greater than would be the case if the formation of such a chemical complex did not occur. Thus, for example, nephrotoxic effects of cadmium are a consequence of its mode of transport to and deposition in the kidney.

Acquisition of data on the uptake, deposition in body tissues, and excretion of cadmium has been achieved through the use of sensitive measurement techniques for the detection of the element in biological tissues. A number of methods are presently available which, when employed in competent laboratories and using good quality control, can reliably measure cadmium at

ultra-trace levels (i.e., at ng/g or ng/m^3 concentrations). At present, atomic absorption spectrometry appears to be the most satisfactory analytical approach for assessing cadmium levels in media of interest for human health evaluations, e.g., urine, blood and tissue levels, as well as in air and foodstuffs. Details of specific analyses used in particular studies involving biological media are included in portions of the Human Epidemiology Chapter (Chapter 3).

1.2.2 Biological and Adverse Health Effects in Man and Animals

Extensive information exists on the acute and chronic effects of cadmium in man and experimental animals. Much of the data on animals, however, is derived from studies utilizing relatively high exposures to cadmium administered by direct systemic injections of the metal; such data, while often of questionable environmental relevance, are valuable in delineating the upper range of toxicological effects in a number of organ systems. Also, once high exposure effects have been demonstrated, follow-up studies have been conducted in some cases to define dose-effect relationships at much lower levels of exposure and, at times, by means of inhalation or oral routes of exposure.

Adverse health effects observed in experimental animals exposed to high cadmium levels include serious acute or chronic damage to several organ systems. Among the more dramatic types of high exposure effects are morphological or functional signs of: renal damage, testicular necrosis, injury of the pulmonary tract, embryotoxic and teratogenic responses, endocrine system derangement, experimental hypertension and related cardiovascular responses, anemia, hepatotoxicity, carcinogenesis and mutagenesis, and reduced immunological responses. Such effects have been most consistently demonstrated to occur after single intraperitoneal or subcutaneous injections of various cadmium

salts in solution and at dose levels exceeding 0.5 to 1.0 mg Cd/kg body weight.

Only a few of the above types of damage, usually of much reduced severity, have been produced in experimental animals with lower, chronic cadmium exposures. Probably the most typical and severe effect of chronic low level cadmium exposure is renal damage. More specifically, cadmium affects the reabsorption capacity of the proximal tubules in the kidney, initially inducing increased urinary excretion of low molecular weight proteins. Thus, tubular proteinuria is one of the earliest signs of chronic cadmium intoxication. Progressively more severe damage to the kidney results from continued exposure, producing aminoaciduria, glucosuria and phosphaturia as later signs of more advanced renal damage. Significant morphological changes accompany these biochemical signs of renal dysfunction and include: diffuse scarring of peritubular capillaries, interstitial edema, adhesions between Bowman's capsule and glomerular capillaries, and tubular atrophy. One or more of these functional and morphological signs of renal damage have been observed in rats and rabbits with prolonged oral exposure to cadmium over periods of weeks or months, starting at exposure levels of 2 ppm or 10 ppm in the drinking water. Kidney cortex cadmium levels at which definite signs of severe kidney damage are observed in animals have been reported to fall in the range of 150 to 450 μg Cd/g wet weight.

Additional of health effects have been observed in animals with long-term exposure to cadmium. For example, significant reductions in birth weights have been reported for offspring born to female rats exposed via inhalation to cadmium sulfate (at 3 mg/m^3) for seven months or to cadmium chloride in the diet (at 200 ppm). The reductions in birth weights appear to result from

cadmium effects on maternal and fetal nutritional status and likely occur secondarily to reductions in fetal copper, iron and zinc levels.

Significant immune suppression effects have also been observed with oral exposures of mice and rabbits to cadmium chloride in drinking water (at levels as low as 10 ppm in that medium) for periods of 5 to 10 weeks. Such immune suppression effects have been observed in the absence of other more classic signs of cadmium toxicity, e.g., indications of renal damage, and may represent heretofore unrecognized "subclinical" effects of chronic low level cadmium exposure. Some experimental evidence suggests that immune suppresssion effects may at times persist beyond the cessation of exposure to cadmium.

The literature relevant to man deals with both acute and chronic health effects arising from cadmium exposure. Much of the data is derived from occupational settings and responses of populations residing in geographic areas of demonstrated high cadmium pollution.

In human beings, acute effects of cadmium generally result from occupational exposure via inhalation. The chief clinical feature of acute cadmium inhalation exposure is pneumonitis, i.e., pulmonary congestion and edema. Individuals who survive this acute episode regain partial lung function but appear to have a higher probability of subsequently dying of chronic pulmonary insufficiency. The inhalation of approximately 1 mg/m^3 of cadmium over an 8 hour period gives rise to clinically evident symptoms in sensitive individuals, whereas an air level of 5 mg/m^3 inhaled over the same time period can be lethal. At much lower exposure levels, in the range of 1 to 100 ng/m^3, no acute exposure effects appear to occur. Rather, the main risk associated with such air levels arises from secondary contamination of water or soils that may increase cadmium levels entering the human food chain.

Chronic adverse health effects of cadmium in man consist chiefly of effects on the renal system and the respiratory tract. The renal effects have been well documented as a systemic index of toxicity outside of occupational settings; chronic respiratory effects, in contrast, are mainly seen in cadmium workers who experience long, steady exposure to the element. The kidney is therefore considered the main target organ affected by chronic cadmium exposure, with renal dysfunction being the "critical effect" manifested by tubular proteinuria at first, followed by aminoaciduria, glycosuria, and other signs of more severe kidney damage if exposure is continued at the same level.

Cadmium-induced tubular proteinuria can be distinguished biochemically from other types of renal dysfunction by the elevated excretion of the protein β_2-microglobulin, and a number of studies have shown that this protein is elevated many-fold in cases where cadmium played a clear-cut role in renal dysfunction. It has been demonstrated that the prevalence of proteinuria increases with age and/or duration of cadmium exposure.

Disturbances in kidney function also exert their effects on bone and mineral metabolism, via effects on calcium and phosphorus, extreme examples of which are osteoporosis and osteomalacia. Itai-Itai or "Ouch-Ouch" disease, observed in Japan is essentially renal tubular dysfunction with osteoporosis and osteomalacia. Additional secondary effects of renal dysfunction are kidney stones, observed in Swedish workers exposed to cadmium; and osteomalacia, in French workers.

It should be emphasized that, once renal tubular dysfunction has proceeded to the point of pronounced proteinuria, it is essentially irreversible. Also, there is considerable evidence, both from human and animal studies, that such irreversible damage typically occurs when cadmium

levels in the kidney cortex exceed approximately 200 μg/g wet weight, especially under conditions of continued exposure (see Risk Assessment Summary).

The chief chronic pulmonary effect of cadmium appears to be centrolobular emphysema and bronchitis resulting from several years of occupational exposure to cadmium oxide fumes, cadmium oxide dust, and cadmium pigment dust. Lung impairment is possible at cadmium oxide fume levels below 100 $\mu g/m^3$ of work place air, depending upon exposure time.

As for other health effects, although hypertension has been demonstrated in laboratory animals chronically exposed through the diet, there is presently no conclusive evidence that cadmium is an etiological factor in human hypertension. In addition, only a few effects on the hematopoietic system, chiefly anemia of the iron-deficiency type, have been noted in man, usually under conditions of occupational exposure to cadmium.

At present, few data are available concerning the direct effects of cadmium on human reproduction and development; the few existing data, however, are consistent with results from animal experiments that have yielded evidence of significant reductions in birth weights as a consistent finding after oral exposures of pregnant animals. Apparently, based on human and animal tissue analysis, little cadmium crosses the transplacental barrier *per se*; however, animal studies have shown that cadmium exposure during pregnancy has an effect on zinc and copper levels in the newborn, probably indirectly due to nutritional deficits, such as zinc deficiency, induced by cadmium. Lastly, although teratogenic effects have been demonstrated in animals at high exposure levels, no evidence has yet been advanced for cadmium being a human teratogen.

In regard to possible mutagenic effects of cadmium, some mutagenic effects in animals have been reported to occur with systemic injections of high doses of cadmium or in *in vitro* test systems; but no data are available that demonstrate mutagenic effects with either oral or inhalation exposure of animals. As for the little available data on mutagenicity in man, particularly with long-term exposure, the findings reported are contradictory and no firm conclusions can be reached at this time. The case for cadmium being carcinogenic in animals is supported only by data obtained at high exposure levels achieved via systemic injections. As for carcinogenic effects in man, some evidence suggests that heavily-exposed industrial workers are at higher risk for prostate cancer; on the other hand, there are no data which currently show that cadmium exposure in the general population is in any way associated with prostate cancer.

As indicated above, several well established health effects of cadmium, e.g., renal damage and its secondary consequences, have been shown to be essentially irreversible and can exert a significant negative impact on the health and well-being of humans. Furthermore, there is no medical treatment presently available that can prevent the accumulation of cadmium in the kidney or achieve elimination or reduction of cadmium stored in the kidney or other soft tissues. Thus, minimization of exposure to cadmium is the only effective approach currently available for averting its adverse health effects.

1.3 EFFECTS OF CADMIUM ON HUMAN POPULATIONS

Studies of various population groups that directly relate cadmium exposure to human health effects are required to define the levels of exposure at which the particular population groups demonstrate adverse health effects and to

identify the specific population segments at high risk. At present, only occupationally exposed workers and some population segments residing in areas of high cadmium exposure in Japan have been extensively studied. Using data from these and other studies, a chain of relationships can be defined from exposure to absorption level to adverse health effects for human populations. This can be done by (1) examining the distribution of cadmium sources to which humans are exposed; (2) assessing the levels of cadmium in blood, urine or soft tissues in various human population segments; and (3) correlating these findings with other research demonstrating adverse health effects at various cadmium levels in human tissue.

A number of studies have measured blood, urine, and hair cadmium levels as a function of demographic variability. When considering the relative validity of these studies, it is important to keep in mind the accuracy and precision of the methodology used for measuring cadmium levels. Some methods appear to be more subject to analytical error than others and, in the course of evaluating data at variance with the literature at large, it becomes apparent that at least part of the difficulty arises from deficient cadmium analyses.

"Average" cadmium blood values for the general population in the United States and elsewhere are in the neighborhood of 1.0 μg Cd/dl whole blood or less, while occupational groups usually exhibit considerably higher values. Unfortunately, little data presently exist that clearly relate age, sex, and race to human blood cadmium levels. For example, no obvious age gradient is discernible among children's blood cadmium values, unlike the case with blood lead levels. In contrast, a clear relationship does exist between smoking

status and blood cadmium levels. That is, it has been shown that adult blood cadmium values are invariably higher in the case of smokers. This finding has significance as one indication of smokers being at special risk for cadmium exposure.

It should be noted that blood cadmium values are generally a relatively poor index of chronic cadmium exposure and body accumulation, but rather are best used as indicators of acute high exposures. Urinary cadmium levels, on the other hand, appear to be reasonably good indicators of chronic low level cadmium exposure and body accumulation. In relation to that, regardless of the population groups studied, the urinary excretion of cadmium is seen to be age-dependent, increasing up to about 50 years of age, and then declining. The mean urine cadmium values from various studies generally indicate normal daily urine cadmium excretion levels to be from 1 to 2 μg Cd/day.

A number of studies have evaluated levels of cadmium in hair as an indication of exposure. Some question exists, however, as to the relevance of hair cadmium values in the case of studying general populations with low exposure to cadmium. Also, a number of analytical problems exist with hair analysis, including the problem of external contamination. Since a number of studies have shown no association between hair cadmium levels and the exposure status of their population groups, the utility of hair cadmium levels remains to be demonstrated.

Autopsy studies of cadmium levels in various human tissues have proven valuable in assessing levels of the element in key organs and total body burden. Such studies are of two types: case studies concerned with specific diseases and general population studies. Such studies have shown

that cadmium levels in human kidney and liver increase with age. The values in liver decrease after 60 to 70 years of age, and kidney values level off after 50 years of age. Smokers show higher cadmium levels in organs than non-smokers. As a function of age, kidney values range from 5 μg/g wet weight in the first decade of life up to 100 or more μg/g at 50 years of age; mean values for adults are generally 20 to 40 μg/g. Smoking adds to the renal cadmium burden up to 50 percent or more above the corresponding values of non-smokers. Liver values increase from about 0.2 μg/g wet weight in the first decade of life up to 1.0 μg/g or more at age 70. Smoking also appears to increase liver cadmium values, particularly in the later decades of life.

A number of epidemiologic studies have dealt with areas of high cadmium exposure in Japan, including the main "Itai-Itai" belt area. Such studies identified Itai-Itai disease as a trio of symptoms--renal dysfunction with osteomalacia and osteoporosis--resulting from high cadmium exposure of people with a history of calcium and vitamin D deficiencies. Other areas of Japan having increased cadmium exposures were also studied, with particular reference to the prevalence of proteinuria. Collectively, these studies show that in high-cadmium areas significant numbers of the inhabitants have tubular proteinuria, with such renal derangement increasing with the age of the individuals and the time of residence in areas of high cadmium exposure.

The Japanese experience with Itai-Itai disease is an informative example of the potential widespread health problems that can ultimately result from cadmium contamination of the human food chain via deposition in water and soils used for agricultural purposes. The problem of detecting and coping with continuous cadmium exposure is well demonstrated by the

late appearance of osteomalacia seen in Itai-Itai disease only after several decades of exposure. The Japanese experience also illustrates the difficulty in ending exposures due to heavy contamination of agricultural land, as noted in Chapter 4.

In regard to other cadmium health effects possibly being associated with exposure of specific population groups, the epidemiologic evidence for human hypertension and other cardiovascular diseases does not conclusively implicate any etiological role for cadmium. In particular, investigators who have controlled for smoking status have not shown an independent association between cadmium levels and hypertension. Also, studies focusing on the role of cadmium in producing chronic diseases of the lung other than cancer have virtually all centered on occupational groups and provide few data clearly demonstrating such effects in the general population. More specifically, although autopsy data have shown cadmium levels in tissue to be higher in persons with a diagnosis of emphysema, smoking status has not been controlled for as a confounding factor. Similarly, epidemiologic evidence often cited as implicating cadmium in the induction of prostatic or other cancers in human populations, while suggestive at this time, is not sufficiently strong so as to conclusively establish that the metal exerts carcinogenic effects on humans. Of major importance in evaluating data bearing on the issue is the fact that cadmium exposure has usually been confounded with exposure to other toxic agents, some being known carcinogens, in the pertinent epidemiologic studies.

1.4 HUMAN HEALTH RISK ASSESSMENT OF CADMIUM

1.4.1 Introduction

Summarized above is our current knowledge concerning the biological and adverse health effects of cadmium in man and experimental animals,

drawing on both clinical and epidemiological studies. This information, along with consideration of exposure aspects, is integrated in the last chapter of the present document in order to address the broader issue of risk to public health in the United States posed by cadmium exposure.

Two aspects of such a risk assessment must be considered: exposure aspects and population response. Key questions that must be addressed for exposure considerations include: (1) what are the environmental sources of cadmium in the United States; and, (2) what are the various routes by which cadmium enters the body? In regard to population health aspects, several additional questions must be considered: (1) What are the human biological and pathophysiological responses to cadmium? (2) Do there exist within the general population in the United States or elsewhere certain sub-groups at special risk to the adverse health effects of cadmium? (3) Quantitatively, what is the magnitude of the risk in terms of numbers of individuals potentially exposed to cadmium levels sufficient to induce particular adverse health effects?

1.4.2 Sources and Routes of Exposure

Trace amounts of cadmium are widely distributed naturally in the environment. Much higher amounts of the metal enter the environment, however, as a result of the manufacture, use, or disposal of cadmium-containing products or in the form of contaminants of other substances. Since virtually no recycling of the element occurs, its use is said to be dissipative, i.e., the amount entering the environment equals the amount produced or used. The current amount of cadmium entering the environment yearly in the United States ranges from 2,000 to 5,000 tons. Dissipation of cadmium in the general environment occurs via contamination of air, water and soil.

Ambient air levels of cadmium across the United States are usually in the range of nanograms per cubic meter (ng/m^3); however, much higher ambient air values, around 0.1 $\mu g/m^3$, are at times found in regions of high cadmium production and industrial use. This may be compared to work place levels of about 100 $\mu g/m^3$ of cadmium in air associated with the induction of chronic health effects in cadmium workers. Airborne cadmium, in addition to being inhaled, may contribute to human exposure via secondary contamination of water and soil due to fallout and entry into the human foodchain. A matter of concern in this regard is that future increased fossil fuel use could lead to higher ambient air cadmium levels and, indirectly through soil contamination, to increased cadmium in food crops.

Significant human exposure from cadmium-contaminated water supplies has occurred in some areas of the world, e.g., Japan; and certain waterways in the United States are contaminated with notable amounts of cadmium. Sources of drinking water in the United States, however, generally are not contaminated; in fact extensive surveys of the drinking water supplies of a large number of areas within the United States indicate that the vast majority of these supplies have cadmium levels below the recommended Public Health Service value of 10 parts per billion (ppb) (0.010 mg/l). It would be desirable, however, to determine whether any contamination of drinking water by cadmium from supply distribution systems, particularly household plumbing, occurs.

In soils, cadmium levels reflect geochemical and anthropogenic sources. Man's activities add substantial cadmium to agricultural soils not only via fallout from the air or contamination of irrigation water, but also through intentional application of phosphate fertilizer and the increasing use of

sewage sludge on agricultural land. Background soil levels in rural areas are normally of the order of 0.1 parts per million (ppm), while contaminated agricultural land and soils in urban areas have considerably higher concentrations of 1.0 ppm or more. Furthermore, highly industrialized areas have much higher proximate soil levels of cadmium than do areas where little industrial activity occurs. Of considerable concern is the fact that soil cadmium constitutes the single greatest source of cadmium affecting the general population through introduction of the metal into man's food chain via uptake into food crops consumed by humans or livestock.

Extensive data entailing both food cadmium determination and human tissue analysis, indicate that most adults in the United States, on the average, presently ingest 10 to 50 μg of cadmium in their daily diets. Based on a six percent absorption value in the absence of nutritional deficiencies, this represents an absorbed value of 0.6 to 3.0 μg per person per day from food alone.

It should be pointed out that these values currently apply to existing food levels of cadmium. It is possible that the cadmium content of foodstuffs will increase in the future as a result of use of superphosphate fertilizers. Also, it is possible that food levels may increase as a result of future municipal incineration of high cadmium content sewage sludge or the use of such sludge as agricultural land dressing. In regard to the latter, for example, sludge used for landspreading on agricultural land has been reported to be at times very high in cadmium, ranging up to 1,000 to 3,000 ppm (EPA Multimedia Levels Cadmium, 1977). Thus, given the long residence time of cadmium in soil, without implementation of proper regulatory controls on sewage sludge disposal, dietary cadmium intake would likely rise significantly.

However, guidance currently available from EPA, USDA and state agricultural agencies as well as regulatory controls being developed by the EPA under the Clean Water Act and the Resource Conservation and Recovery Act to directly control land application of wastes such as sewage sludge, may help to minimize any future increase in dietary cadmium levels as a result of applying these wastes to agricultural land.

Increased future use of cadmium-containing fossil fuels should also be considered as a potential source of increased future dietary cadmium levels.

In addition to ingestion of dietary cadmium as the main route of exposure of most Americans, cigarette smoking has been conclusively shown to add greatly to body burdens of cadmium; and heavy smokers may assimilate as much or more cadmium from cigarettes as they do from the diet. Amounts of respiratory intake from cigarettes range from 4 to 6 μg from two packs smoked per day. This demonstrated added intake of cadmium from cigarettes accounts well for higher levels of cadmium consistently found in urine and kidney tissue of smokers by epidemiologic studies.

1.4.3 Human Population Responses to Cadmium in Human Risk Assessment

1.4.3.1 Summary of human health effects of cadmium--As indicated above, human populations are exposed to cadmium via inhalation and ingestion, and the health effects associated with these routes of exposure are generally chronic in nature.

Of most relevance to human populations are chronic respiratory and renal effects of cadmium. Of these two effects, it is more appropriate to consider chronic renal effects, so the kidney (kidney cortex) is considered the critical organ in chronic exposure to cadmium so far as a public risk assessment discussion is concerned.

Tubular proteinuria is the earliest demonstrable marker for renal dysfunction induced by cadmium, with other effects such as aminoaciduria, glycosuria, and hypophosphaturia seen with continued exposure. Renal dysfunction, once manifested clinically in terms of such effects, is often irreversible, as demonstrated by studies on cadmium workers who continued to show renal tubular dysfunction long after cadmium exposure had ceased. Also, cadmium-induced tubular proteinuria is generally accepted as a significant adverse health effect because by the time such an effect is manifested the kidney is already well on the way to increasingly severe damage and has essentially no reserve for protection against other pathological stresses. This vulnerability is reflected in observations of increased health complications among certain cadmium workers subsequent to their first exhibiting renal tubular proteinurea.

According to both clinical-epidemiological and model-calculation data, a kidney cortex level of 200 μg Cd/g kidney can be taken as the critical concentration, i.e., the level of cadmium in the kidney (critical organ) at which the earliest discernible adverse effect (the critical effect of renal tubular proteinuria) can be expected to occur.

1.4.3.2 Dose-effect/dose-response relationships of cadmium--As reviewed in the health effects section of this document, the severity of any given marker effect increases as the level of cadmium exposure increases, and the quantitative aspects of response, i.e., the frequency of occurrence of a stated effect in an organism population, comprises the dose-response relationship.

With cadmium, the usual indicators cannot be used to assess the status of the critical organ, the kidney cortex, in terms of that organ's direct exposure to the insulting agent, because measurements of blood or urine cadmium are not

precise ways to assess the extent to which the kidney is on its way to functional impairment. An alternative strategy has been to define an approximate critical concentration in the kidney cortex above which renal tubular dysfunction can be expected to occur. As was stated earlier, this value is now generally accepted to be 200 μg Cd/g wet weight renal cortex. Using this approach, the probable level of total exposure necessary to produce the critical concentration via ingestion and/or inhalation can then be calculated.

As indicated in the risk assessment section of the document, one may use this approach with two previously calculated half-times of cadmium in the body: 18 and 38 years (see Table 1-1). Furthermore, in that section (4) is determined the daily retention values of cadmium in the body for these half-times and various exposure periods.

For populations at large, the main factor determining the level of daily cadmium retention is daily dietary intake. This is certainly the case with non-smokers; heavy smoking on the other hand, can lead to retention of amounts of cadmium which approach or even exceed that retained from the dietary intake (see Table 1-2).

Calculations, based on metabolic models, regarding levels of daily dietary intake of cadmium necessary to achieve the critical renal cortex concentration of 200 μg/g associated with renal dysfunction, have yielded widely varying estimates for critical dietary intake levels. Thus, dietary intake levels ranging from 200 to 480 μg/day have been projected as being sufficient to eventually induce proteinuria in the 40- to 50-year-old age group. Various epidemiologic studies have yielded data that fit well with various estimates within the above range of theoretical estimates; a Working Group of Experts

Table 1-1. CADMIUM EXPOSURE REQUIRED FOR REACHING A KIDNEY CORTEX CONCENTRATION OF 200 μg Cd/g USING DIFFERENT ALTERNATIVES FOR BIOLOGICAL HALF-TIME IN KIDNEY CORTEX AND EXPOSURE TIME[a]

Basis of calculation[b]	Exposure time (yr)	Levels of cadmium intake or retention yielding renal dysfunction, assuming cadmium half-times of: 38 yr	18 yr
		Daily retention (μg)	
Constant daily retention during whole exposure time	10	36	39
	25	16	20
	50	10	13
		Industrial air concentration ($\mu g/m^3$)	
25% pulmonary absorption, 10 m^3 inhaled per work day, 225 work days/year	10	23	25
	25	11	13
		Daily cadmium intake (μg)	
Food exposure for 50-yr-old person (2500 ca/day) (4.5% retention) (changing caloric intake by age accounted for)	50	250	360
		Corresponding average concentration in foodstuffs (μg/g)	
Total amount (net weight) of food/day 300 g	50	0.8	1.2
600 g		0.4	0.6
1000 g		0.25	0.35

[a]Adapted from Friberg, L. M. Piscator, G. G. Nordberg, and T. Kjellström. Cadmium in the Environment. CRC Press, Cleveland, 1974.

[b]Assumptions: one-third of whole body retention reached kidney and kidney cortex concentration 50% higher than average kidney concentration. From Nordberg, G. F. (ed.). Effects and Dose-Response Relationships of Heavy Metals. Elsevier, Amsterdam, 1976.

Table 1-2. MEDIA CONTRIBUTIONS TO NORMAL RETENTION OF CADMIUM[a]

Medium	Exposure level	Daily retention (μg)
Ambient air	0.03 μg/m^3	0.15
Water	1 ppb	0.09
Cigarettes packs/day	μg/day[b]	
1/2	1.1	0.70[c]
1	2.2	1.41[c]
2	4.4	2.82[c]
3	6.6	4.22[c]
Food	50 μg/day	3.0

[a]Source: Deane, L. G., D. A. Lynn, and N. F. Surprenant. Cadmium: Control Strategy Analysis. ECA Cong., Bedford, Mass. U.S. Environmental Protection Agency. 1976.

[b]Based on 0.11 μg per cigarette.

[c]Assumes a 64% retention rate.

for the Committee of European Communities (CEC), however, has tentatively concluded that 200 to 248 μg/day is the best estimate of daily dietary intake necessary to reach the renal critical concentration of 200 μm/g in kidney cortex over a 50 year exposure period for nonsmokers. For smokers, a level of dietary intake of 169 μg/day was estimated as being sufficient for the critical renal cortex concentration to be reached.

The above approaches are aimed at estimating "threshold" dietary intake values necessary to produce a critical cadmium concentration in renal cortex associated with the critical effect of renal tubular dysfunction. Such approaches, however, may not adequately take into account individual biological variability in terms of dietary levels yielding significant renal dysfunction; this is suggested by certain recently published studies on dose-response relationships that relate dietary cadmium intake levels to numbers of individuals in study populations showing increased proteinuria over background levels.

In regard to such dose-response aspects of cadmium exposure, i.e., defining that proportion of a target population that would be expected to show a given health effect at a particular level of cadmium exposure, there exist both modeling and empirical data (see Chapter 4) which have been recently compiled into a dose-response framework. Using renal tubular damage as the adverse health effect for which response rates were calculated and daily dietary intake of cadmium as the exposure variable, the theoretical framework predicts increasing response rates for renal damage as a function of dietary intake of cadmium. As illustrated in Table 1-3, a daily dietary intake of 60 μg/day, for example, would be predicted to produce, by age 50, a renal damage response in 1.0 percent of this age-group population. Further, at daily cadmium intake rates of 80 and 100 μg/day, approximately 2.5 percent and 5 percent of the population, respectively, would be predicted to sustain renal tubular injury.

Actual, observed prevalence rates in several epidemiologic studies match well the predicted rates; due to the small number of observations at lower dietary intake levels, however, little confidence can yet be placed in rates indicated for dietary levels under 80 to 100 μg/day.

The data in Table 1-3 describe dose-response relationships for non-smokers and individuals with "average" dietary habits. In the case of smokers the total cadmium retention from both diet and smoking increases and, based on data discussed in Chapter 4, heavy smokers could conceivably have a consequently greatly increased response rate over non-smokers. Similarly, for individuals, such as vegetarians, having certain idiosyncratic dietary habits that likely

Table 1-3. FOOD EXPOSURE; CALCULATED INTAKES (μg Cd/day) THAT MAY GIVE A CERTAIN RESPONSE RATE AT AGE 50[a]

	Response rate (proportion) with renal tubular dysfunction					
	0.1%	1%	2.5%	5%	10%	50%
Europeans, body weight 70 kg.	32	60	80	100	148	440
Japanese, body weight 53 kg.	24	44	60	76	100	325

Gastrointestinal absorption rate 4.8%; Non-smokers, from Kjellström, T. Comparative study of Itai-Itai disease. In: Cadmium 77: Edited Proceedings, First International Cadmium Conference. Metal Bulletin Ltd., London, 1978. pp. 224-231.

lead to higher than "average" dietary intake of cadmium, there may exist a greater risk for increased response.

1.4.3.3 Populations at Risk to the Adverse Health Effects of Cadmium--Populations at risk are those segments of a defined population exhibiting characteristics associated with a significantly higher probability of developing an abnormal condition, illness, or status. This enhanced risk may come about because of some greater inherent susceptibility or from exposure situations peculiar to that group.

In the case of cadmium, based on the collective experience with widespread exposure in Japan and other data cited in this document, certain large segments of the United States population can be identified as likely being at risk for experiencing adverse health effects associated with exposure to the metal. Generally speaking, other than for certain occupationally exposed workers, acute toxic effects of cadmium are not of much concern in assessing its potential public health impact in the United States. Rather, chronic effects, mainly renal dysfunction or damage, are of primary concern due to the propensity of cadmium to accumulate in the body (especially in the kidney) over very long time periods, e.g., for 40 to 50 years or more.

Given the fact cadmium is retained in the kidney over long time periods, then it is not surprising that older segments of various populations studied (i.e., those over 45 to 50 years of age) have generally been found to have the highest levels of cadmium in the kidney and also to display the highest incidence of renal dysfunction. Based on this, it would appear that those individuals in the United States population over 40 to 50 years old are most immediately at risk for exhibiting cadmium-induced renal dysfunction as a

consequence of further cadmium exposure. Also, given the dependence of cadmium absorption on nutritional factors, e.g., increased uptake in the presence of iron, zinc, or calcium defiency, the risk would be greatest among those older Americans who are poorly nourished.

It is obviously the case that aging affects all members of any population and, in view of that, the entire population of the United States must therefore be viewed as being at potential risk for adverse effects associated with cadmium exposure. In fact, due to the accumulation of cadmium in the kidney essentially over an entire lifetime, present cadmium exposure levels and any future increments in exposure, in the long run, would be expected to impact most heavily on present younger members of the population. Thus, any assessment for the American public of potential risk associated with cadmium exposure must attempt to project the likely eventual consequences of present and/or increased cadmium exposure levels for the general United States population. In attempting to make such projections, dietary cadmium intake, as the chief source of cadmium for the general public, is of primary concern in the analysis.

In regard to current daily dietary cadmium intake levels for Americans, different estimates have been generated depending upon the measurement approaches employed. FDA "market basket" surveys, for example, have yielded estimates ranging from approximately 30 to 50 μg/day, or even around 70 μg/day for teenage males. On the other hand, estimates based on fecal cadmium excretion measurements tend to be much lower, i.e., with mean dietary intake for non-smokers being around 18 μg/day with a standard deviation of approximately 8 μg. Taking that degree of variability into account and comparing the fecal excretion-derived estimates in relation to the above market basket survey-derived estimates, it seems reasonable to state that current American daily

dietary cadmium intake levels, on the average, fall within the range of 10 to 50 μg/day.

It is next necessary to compare the above estimate(s) of current daily dietary cadmium intake with ingestion levels that, over an extended period of time (40 to 50 years), will lead to sufficient cadmium being accumulated in the kidney so as to induce the critical effect associated with chronic cadmium exposure, i.e., renal tubular dysfunction. As noted earlier in the present summary and discussed in more detail in Chapter 4 of this document, various modeling approaches have yielded estimates ranging from 200 to 480 μg/day as the requisite ingestion level eventually resulting in the critical renal cortex cadmium concentration of 200 μg/g wet weight being reached and, thus, associated renal dysfunction occurring. Also as noted earlier, a concensus of opinion among a group of experts working for the Committee of European Communities (CEC) was that 200 to 248 μg/day is probably the best estimate of the critical daily cadmium ingestion level necessary to induce renal dysfunction. If the latter view is accepted, then average American dietary cadmium intake levels of 10 to 50 μg/day would be from approximately 4 to 25 fold less than ingestion levels estimated to yield renal dysfunction over a 50 year exposure period. For some individuals with distinctly higher than average dietary cadmium intake levels, however, that margin could be significantly less.

Certain empirically obtained data suggest that attempts at defining a single daily ingestion level eventually yielding renal dysfunction as a consequence of a critical renal cortex cadmium concentration being reached may not adequately take into account individual variability in rates of uptake and retention of cadmium. Projections based on dose-response data relating measured dietary cadmium intake levels to observed prevalence of renal proteinuria, in fact, suggest that 1, 2.5, and 5 percent of the American

population would exhibit renal dysfunction at daily dietary cadmium ingestion levels of 60, 80, and 100 μg/day. Viewed from that perspective, current daily dietary cadmium intake level(s) of 10 to 50 μg/day for Americans may not provide even a two-fold margin of safety before a small (1 percent), but significant, portion of the general United States population would be expected to experience cadmium-induced renal dysfunction.

Furthermore, based on data discussed previously, cigarette smokers constitute a large population at still greater risk than the general public. In regard to increased risk for smokers, tabulations have been carried out in an effort to demonstrate the relative contribution of cigarette smoking to the total daily added burden of cadmium (daily retained cadmium) as a function of the amount of cigarettes consumed (see Table 1-4). For example, assuming a 25 μg/day daily dietary intake level, smoking one, two, or three packs of cigarettes daily can contribute as much or more than the average level of cadmium retained due to dietary ingestion, as illustrated in the table. When the amounts of cadmium retained daily in individuals who smoke heavily are compared to critical daily retention values (10 μg/day) above which the critical concentration of cadmium in kidney will eventually be exceeded, the relative margin of safety for exposure to other sources of cadmium is significantly reduced. Thus, at present, cigarette smokers who constitute a large portion of the United States population are at greater risk for cadmium-induced renal dysfunction than non-smokers.

A third group at possible risk for adverse health effects of cadmium are those with unusual dietary habits, such as vegetarians and those consuming large quantities of shellfish (e.g., oysters) over an extended period of time. These groups would be at even greater future risk in the event that cadmium

Table 1-4. ESTIMATED RELATIVE CONTRIBUTION OF DIETARY INTAKE, CIGARETTE SMOKING AND AMBENT AIR CADMIUM LEVELS TO TOTAL DAILY CADMIUM RETENTION FROM ALL SOURCES[a]

Dietary Intake (Net Retention)	Smoking Status (Net Retention)	Air Cadmium Levels (Net Retention) 0.0 ng/m^3 (0.0 mg/day)	1.0 ng/m^3 (.0005 mg/day)	10 ng/m^3 (.005 mg/day)	100 ng/m^3 (.05 mg/day)	1000 ng/m^3 (0.5 mg/day)
Food Level A = 25 mg/day (1.50 mg/day)	Non-smoker (0.00 mg/day)	1.590 (0;0%)*	1.591 (0;0%)	1.595 (0;0%)	1.630 (0;3%)	2.090 (0;24%)
	½ pack/day (0.70 mg/day)	2.290 (31;0%)	2.291 (31;0%)	2.295 (31;0%)	2.330 (30;2%)	2.790 (25;18%)
	1 pack/day (1.41 mg/day)	3.000 (47;0%)	3.001 (47;0%)	3.005 (47;0%)	3.050 (46;1%)	3.500 (40;14%)
	2 pack/day (2.82 mg/day)	4.410 (64;0%)	4.411 (64;0%)	4.415 (64;0%)	4.460 (63;1%)	4.910 (57;10%)
	3 pack/day (4.22 mg/day)	5.810 (73;0%)	5.811 (73;0%)	5.815 (73;0%)	5.860 (72;1%)	6.310 (67;8%)
Food Level B = 50 mg/day (3.00 mg/day)	Non-smoker (0.00 mg/day)	3.090 (0;0%)	3.091 (0;0%)	3.095 (0;0%)	3.140 (0;2%)	3.590 (0;14%)
	½ pack/day (0.70 mg/day)	3.790 (18;0%)	3.791 (18;0%)	3.795 (18;0%)	3.840 (18;1%)	4.290 (16;12%)
	1 pack/day (1.41 mg/day)	4.500 (31;0%)	4.501 (31;0%)	4.505 (31;0%)	4.550 (31;1%)	5.000 (28;10%)
	2 pack/day (2.82 mg/day)	5.910 (48;0%)	5.911 (48;0%)	5.915 (48;0%)	5.960 (47;1%)	6.410 (44;8%)
	3 pack/day (4.22 mg/day)	7.310 (58;0%)	7.311 (58;0%)	7.315 (58;0%)	6.360 (57;1%)	7.810 (54;6%)
Food Level C = 75 mg/day (4.50 mg/day)	Non-smoker (0.00 mg/day)	4.590 (0;0%)	4.591 (0.0%)	4.575 (0;0%)	4.640 (0;1%)	5.090 (0;10%)
	½ pack/day (0.70 mg/day)	5.290 (13;0%)	5.291 (13;0%)	5.295 (13;0%)	5.340 (12;1%)	5.790 (12;9%)
	1 pack/day (1.41 mg/day)	6.000 (24;0%)	6.001 (24;0%)	6.005 (24;0%)	6.050 (23;1%)	6.500 (22;8%)
	2 pack/day (2.82 mg/day)	7.410 (38;0%)	7.411 (38;0%)	7.415 (38;0%)	6.460 (38;1%)	7.910 (36;6%)
	3 pack/day (4.22 mg/day)	8.810 (48;0%)	8.811 (48;0%)	8.815 (48;0%)	8.860 (48;1%)	9.310 (45;5%)

*Each first value equals total daily cadmium retention levels (in mg/day) from all sources, assuming constant daily retention from water of 0.09 mg/day derived from consumption of water with cadmium concentration of 1 ppb. The two values in parentheses ( ) indicate percentage of total daily cadmium retention attributed to cigarette smoking and ambient air cadmium exposure, respectively, at a given ambient air cadmium level.

[a]Note that daily cadmium retention of 10 mg/day would be projected to result in a critical cadmium concentration of 200 mg/g wet weight of kidney coretx being reached over a 50-year exposure period, assuming a kidney half-time for cadmium of 38 years.

levels in their preferred foodstuffs were to substantially increase in the future.

One could also hypothesize that children may be another population segment at potential risk due to increased exposure or absorption of cadmium. Such increased risk, however, is questionable in terms of projected lifetime tissue accumulations of cadmium except in cases where unique behavior patterns of children, e.g., mouthing of non-food objects, bring them into contact with cadmium-contaminated house dust or soils.

1.4.4 Overall Conclusions

Uptake of cadmium in man via a variety of routes of exposure can result in serious adverse health effects. These include significant irreversible pulmonary and renal damage that typically occur as a result of chronic occupational and non-occupational exposure.

The levels of chronic cadmium exposure necessary to induce significant renal dysfunction, the "critical effect" typically observed earliest with ambient environmental exposures, may not exceed by much the levels presently encountered through "average" dietary intake by many Americans. Thus, increases in cadmium exposure from whatever source will reduce an already low margin of safety before adverse effects are seen.

Possible sources of exposure that can be identified as presently contributing additional burdens of cadmium include cigarette smoking as well as high air levels encountered in some industrial settings. As for ambient air as a possible source of increased environmental cadmium exposure, calculations summarized in Table 1-4 suggest that, in general, ambient air exposures below 10 ng/m^3 do not result in any increased kidney cortex concentration of cadmium.

However, as discussed in Chapter 4 under Exposure Sources, ambient air levels of cadmium in the vicinity of certain industrial facilities have been observed to exceed 10 ng/m^3 and, at times, to approach 100 ng/m^3, a point at which significant accumulation of cadmium occurs.

Several recent developments in waste management, energy production, and food production appear to have the potential for markedly changing the present United States population exposure profile for cadmium. Specifically, substantially increased ambient air levels of cadmium could result from future uncontrolled expanded municipal incineration of solid waste materials and expanded fossil fuel use, especially increased coal combustion. Also, future uncontrolled expanded agricultural use of cadmium-contaminated phosphate fertilizers or high-cadmium content sewage sludge could potentially introduce increased amounts of cadmium into the human food chain and thereby raise levels of dietary cadmium.

In view of the above, regulatory action addressing any single source of exposure, but not taking into account all other possible sources of exposure and expected changes in levels resulting from them, is likely to be inadequate in terms of truly safeguarding the public health. Instead, a well-coordinated comprehensive plan for controlling exposure of the general population would be desirable; it would be prudent to have as an overall goal the objective of reducing total cadmium exposure from current levels rather than allowing exposure to rise. Realistically, this would probably require control at many points along the dissipation pathway for the element: from mining and smelting operations, through industrial manufacturing processing or other utilization as in fossil fuel or phosphate fertilizer usage, to ultimate disposal of

cadmium-contaminated wastes. In the absence of effective control procedures, gradually increasing environmental contamination, especially of agricultural soils, should be expected to occur. Also, as demonstrated by the Japanese experience with cadmium contamination of agricultural soils, once significant soil contamination with cadmium does occur, then it is virtually impossible to reverse and may ultimately result in the loss or restricted use of large tracts of farm land (see Exposure Aspects, Chapter 4).

The cost of uncontrolled environmental exposures to cadmium in terms of populations at risk, it should be noted, could be immense. The populations most at risk include: (1) older people, who number in the millions and whose numbers are growing; (2) smokers, who also number in the millions and whose ranks will probably continue to be filled by virtue of expanding numbers of teenagers who smoke; (3) people with dietary habits that result in consumption mainly of food groups (e.g., grains, leafy vegetables, and beef kidney and liver) with comparatively high cadmium content; and (4) children, during both pre- and postnatal development.

2. BIOLOGICAL SIGNIFICANCE AND ADVERSE HEALTH EFFECTS OF CADMIUM

2.1 INTRODUCTION

A variety of biological and adverse health effects have been documented in both man and experimental animals under conditions of acute and chronic exposure to cadmium. These responses are discussed in this section.

From the standpoint of relevance of these effects to the hazards posed by cadmium on populations at large, the chronic effects are considerably more important than those of an acute nature. In turn, those chronic effects elicited by ingestion of the element are probably of more significance than that by inhalation, although this should not be taken to mean that the opposite might not be the case in certain situations. Studies involving the parenteral administration of the metal to experimental animals are also included because they are potentially valuable in defining the metabolic and toxic parameters of cadmium.

Assessment of the effects of an element follows closely on an understanding of the element's metabolism in an organism. Therefore, the first section of this report deals with the absorption, transport, distribution, and excretion of cadmium in man and animals.

Systemic effects of cadmium are, in large measure, macroscopic manifestations of injury at the cellular, subcellular, and molecular level. Thus, enzymological, subcellular and cellular studies, both *in vivo* and *in vitro*, are discussed first along with consideration of the role of metallothionein. Studies of the effects of cadmium on various specific organ systems are reviewed and evaluated next. Special attention is accorded the renal, pulmonary, cardiovascular, and reproductive systems.

Also discussed are endocrine, skeletal, hepatic, gastrointestinal, neural, and immunosuppressive effects of the metal.

No toxic element functions in a metabolically static milieu, and this is especially true of cadmium. Therefore, discussion of the effects of cadmium should take into account various interactions between cadmium and other elements which either ameliorate or potentiate its effects. This includes, for example, cadmium/zinc, cadmium/selenium, and cadmium/iron relationships. The interactive effects of these metal/metal combinations are discussed in a separate, final section in addition to being alluded to in other sections where appropriate.

2.2 METABOLISM OF CADMIUM

No discussion of the health effects of a toxic substance is complete without consideration of the metabolism of that element, i.e., the processes of absorption, transport, deposition, remobilization in organs, and excretion.

While a sizable body of data exists on the quantitative and qualitative aspects of cadmium metabolism in man and experimental animals, the present report is concerned with those features of cadmium metabolism that impinge directly on health effects and is not meant to be an exhaustive review of the relevant literature.

2.2.1 Sources of Exposure

Cadmium, like other multimedia environmental contaminants such as lead, is introduced into the host organism from several sources including air, food, and water. Information on amounts of cadmium encountered in various media is considered later in a separate section on exposure in the risk-assessment portion of the present report.

2.2.2 Inhalation

Factors that require consideration in dealing with pulmonary absorption include the physiochemical features of the form of airborne cadmium at the time of external exposure, as well as subsequent handling of the deposited form of cadmium in the respiratory tract. The extent of deposition in the various pulmonary tract compartments is a function of particle size and solubility. The quantitative features of this relationship have been reviewed by the Task Group on Lung Dynamics (1966), Fulkerson and Goeller (1973), Friberg et al. (1974), and Nordberg (1974). Cadmium-containing matter (usually aerosols) in air is lodged in the lungs and the tracheobronchial tract in quantities inversely related to particle size; lung deposition is about 50 percent for particles of 0.1 micrometer mean mass diameter (MMD) ranging down to 10 percent for particles with an MMD of 5 micrometers. Deposition in the nasopharyngeal tract, on the other hand, is a direct function of particle size.

Part of the inhaled material deposited in the respiratory tract undergoes retropassage via ciliary activity and is then swallowed. Factors governing this portion of the intake are therefore related to gastrointestinal absorption, which is discussed below. Many of the earlier studies on retention time of inhaled cadmium in the form of aerosols or fumes are not amenable to interpretation due to lack of knowledge about particle size. The Task Group on Lung Dynamics (1966), however, has arrived at a half-time range of several days to a year for retention of cadmium in the lung. Systemic absorption from the lung of inhaled cadmium is estimated for man to range from less than 20 to 50 percent, depending on particle size, solubility of the cadmium compound, etc. Animal studies

provide figures of 10 to 40 percent (Friberg et al., 1974; Elinder et al., 1976; WHO, in press).

2.2.3 Gastrointestinal Absorption

Human populations generally acquire the major part of their cadmium intake from the diet and some from water. The amount of such intake is discussed elsewhere in this report. The extent of gastrointestinal absorption of ingested cadmium in man is about six percent; it is somewhat less in animals (Friberg et al., 1974; Nordberg, 1976). Dietary factors, as well as the chemical form of the metal, play a role in modifying this figure, with certain nutritional deficiencies leading to an enhancement of cadmium absorption in man and animals (Friberg et al., 1974). As a specific example, the group most affected with the symptomatology of Itai-Itai disease in Japan were women who had a history of Vitamin D and calcium deficiency (see Health Effects and Epidemiology sections).

2.2.4 Other Absorption Routes

Two other routes of absorption may potentially play a role in the exposure of humans to cadmium: cutaneous absorption and transplacental transfer. Cutaneous cadmium absorption has been shown in animals (Skog and Wahlberg, 1964; Wahlberg, 1965; Kimura and Otaki, 1972); however, this route is probably minor in man compared to inhalation and ingestion. Transplacental transfer is discussed in the Reproduction and Development section (2.7) of this chapter.

2.2.5 Transport and Deposition

Blood is the vehicle for transport of cadmium via inhalation or ingestion and the kinetics of its movement in the body rest heavily on the type of exposure (Friberg et al., 1974). What constitutes "normal" blood levels

of cadmium is a subject of controversy as is discussed later in the Risk Assessment section (4.). In the general population, more cadmium is found in plasma than erythrocytes; with increasing exposure, however, the ratio shifts toward higher amounts being found in the erythrocytes (Friberg et al., 1974).

Animal studies (Friberg et al., 1974) show that, in the time immediately following parenteral administration of cadmium ion, most of blood cadmium is found in plasma. Furthermore, there is initially a rather rapid clearance of cadmium from blood. This is followed by a slower decline and a subsequent rise in in the Cd content of both plasma and cells, with a larger comparative amount accumulating in the erythrocyte. This increase corresponds to the time required for enhanced metallothionein synthesis. The half-time of blood cadmium following cessation of a chronic exposure appears to be about six months (Friberg et al., 1974).

Much data exist on the relative distribution of cadmium among various organs in man and experimental animals and these have been reviewed (Friberg et al., 1974; Nordberg, 1972). In populations with minimal exposure to cadmium, about half of the organ distribution of cadmium is in liver and kidney, with kidney accounting for 30 percent of the total body burden. A higher proportion of cadmium is found in liver during chronic exposure because of cadmium-induced synthesis of metallothionein in the liver.. Other organs that accumulate cadmium include the testes, lungs, pancreas, spleen, and various endocrine organs. In contrast, relatively low concentrations of cadmium are found in bone, brain, and muscle tissue. However, due to the much greater mass of muscle versus liver and kidney tissue, the

absolute amount of cadmium found in muscle within a given mammalian organism can be considerable.

Simple model projections for the half-time value for cadmium in various organs predict, for example, a value between 17.6 yr (Tsuchiya and Sugita, 1971) and 38 yr (Kjellstrom, 1971) for kidney and kidney cortex in man. Although these values were derived from data on representative samplings of Japanese and American populations, Nordberg (1976) has cautioned that they involved use of a simple model dependent on a fixed fraction of cadmium directly transferred to kidney, whereas the true picture is rendered more complex by hepatic-renal transfer of cadmium. Nevertheless, the simple model is still useful for most practical purposes.

Metallothionein, it should be noted, plays a major role in the movement and excretion of cadmium _in vivo_ in various species. Details concerning this cadmium-binding protein are presented in a subsequent section (section 2.3.2).

2.2.6 Excretion

Excretion of cadmium by man and experimental animals is mainly via the urinary and gastrointestinal tracts. Since only about six percent of cadmium is absorbed from the gastrointestinal tract, the bulk of ingested cadium is lost in feces. Thus, it is difficult to assess the relative differential excretion of absorbed cadmium by the renal and intestinal routes. Renal excretion in the urine, nevertheless, is of a magnitude such that it can be taken as a relatively good indicator of internal exposure. Urinary output is seen to increase slowly with age as the cadmium body burden increases. In the presence of renal dysfunction, however, urinary levels of cadmium may rise markedly. That is, in both animals and man, it

has been observed that only relatively small amounts of cadmium are excreted in the urine early in exposure, but sudden increases then occur concomitantly with the appearance of proteinuria or other signs of renal damage (Friberg, 1952; Axelsson and Piscator, 1966; Nordberg and Piscator, 1972; Suzuki, 1974; Friberg et al., 1974; Lauwerys et al., 1974; Singerman, 1976).

In man, under conditions of low-level, chronic cadmium exposure, cadmium loss via the urine is typically < 1 μg/day (Johnson et al., 1977; Elinder et al., 1978) for non-smokers. For smokers and other cadmium-exposed individuals, urinary cadmium values are higher; and there appears to be some overall relationship between urinary excretion of cadmium and total body burden. While it has been demonstrated that biliary excretion occurs in animals, it has yet to be demonstrated that it is a significant factor in man (Stowe, 1976; Cherian, 1977; Cherian and Vostal, 1977).

2.3 SUB-CELLULAR AND CELLULAR ASPECTS OF CADMIUM TOXICITY

Various studies focusing on the toxic effects of cadmium at the cellular and sub-cellular level are discussed in this section. Types of effects discussed include: (1) general subcellular effects, e.g., the interaction of cadmium with enzymes and non-enzymic biomolecules crucial to the physiological functioning of the organism and (2) the induction of metallothionein and its role in cadmium metabolism and toxicity.

2.3.1 General Sub-Cellular Effects

The literature on the interaction of cadmium with enzymes spans a spectrum of effects, ranging from the observation of nonspecific activation or inhibition of purified enzyme preparations in vitro to enzymic effects that constitute a significant part of the in vivo pathology of cadmium.

Since much of the former tends to have little relevance to in vivo conditions, much of the data is not given detailed consideration here. Rather, one is directed to a more general review, such as that of Vallee and Ulmer (1972). In some cases, it is more appropriate to discuss enzyme effects as part of the systemic toxicity of cadmium; this is done elsewhere in this report.

There are several mechanisms by which cadmium may influence enzyme function. The metal ion may interact with the enzyme directly via the marked affinity of cadmium for the sulfhydryl and imidazolyl nitrogen groups at sites necessary for enzyme function and may even substitute for native metal ions in various metalloenzymes, as in the case of substituting for zinc in zinc metalloenzymes. Similarly, cadmium may interact with the substrate for an enzyme, sufficiently perturbing the conformation to markedly alter enzyme-substrate binding kinetics. Circulating levels of enzymes may also be altered due to organ derangement and cellular release, as in the case of changes in marker enzymes for hepatic function. Another important mechanism, particularly in cases of zinc deficiency, may be alterations in the pattern of distribution of zinc.

Virtually all of the studies dealing with the cellular and sub-cellular aspects of cadmium toxicity have involved experimental animals. In Table 2-1 are tabulated the various effects reported, divided as to whether the studies were in vivo or in vitro in nature. In the text, in vivo and in vitro studies are discussed together under the different types of subcellular effects or sites studied. It should be noted that many of the dosages employed are well above what might be encountered by man.

A number of reports indicate that cadmium has an effect on metabolizing enzymes of organisms. For example, Furst and Mogannam (1975) have reported

Table 2-1. SUBCELLULAR AND CELLULAR CADMIUM TOXICITY IN EXPERIMENTAL ANIMALS

Species	Cd Dose*	System(s) studied**	Effect(s) found**	Reference
In vivo Studies				
Rat	2.5 or 3.8 mg/kg b.w.; i.p.	Hepatic drug-metabolizing enzymes	25 to 60% inhibition of aniline hydroxylase and nitro reductase activity; 50% reduction of microsomal P-450 content	Teare *et al.*, 1977
Rat	2.0 mg/kg b.w.; single; i.p.	Hepatic drug-metabolizing enzymes	24% increase in hexobarbital sleeping time; 27% reduction in cytochrome P-450; 44% reduction in cytochrome b_5; 57% inhibition of amino pyrine demethylase (3rd day post-injection); 32% aniline hydroxylase inhibition of (3rd day post-injection)	Krasny and Holbrook, 1977
Mouse	5 and 3 mg/kg b.w.; i.p.; after i.p. injection of 3 methyl cholanthrene/ octanoin solution	Hepatic drug-metabolizine enzymes	Total inhibition of AHH activity at higher dose; little inhibition of AHH activity at lower dose	Furst and Mogannam, 1975
Rat	0.25 and 1.0 mg/kg b.w.; i.p. daily for 21 or 45 days	Cyclic AMP and associated enzymes	Increase in cyclic AMP level; increase in both basal and fluoride-stimulated activity	Singhal *et al.*, 1976

Table 2-1. SUBCELLULAR AND CELLULAR CADMIUM TOXICITY IN EXPERIMENTAL ANIMALS (CONTINUED)

Species	Cd Dose*	System(s) studied	Effect(s) Found**	Reference
Rat	100 ppm in drinking water; ad lib. for 30 days	Enzymes of duodenal mucosa	Decrease in brush-border ATP-ase activity; decrease in alkaline phosphatase activity; increase in isocitrate dehydrogenase activity; increase in G-6-PD activity	Sugawara and Sugawara, 1975
Rat	3.2 mg/kg (0.03 m mole/kg); single i.p.	Dehydrogenase enzyme activity	89% inhibition of succinic dehydrogenase activity in liver and testis; increase in lactate dehydrogenase activity	Singh and Nath, 1975
Rat	300 ppm in drinking water; ad lib.	Osidatine phosphorylation	Reduction in respiration and P/O ratios; increase in mitochondrial cytochrome A and cytochrome C	Kamata et al., 1976
Rat	0.34 to 3.4 mg/kg b.w.; i.p.	RNA synthesis in hepatic fractions	Inhibition of RNA synthesis in hepatic nuclei; significant inhibition of polyuridylic acid-directed incorporation of L-(^{14}C)-phenylanine in microsomes	Stoll et al., 1976
Rat	2 mg/kg b.w.; once per wk.; for 2 to 3 wk.	Protein synthesis by ribosomes	Inhibition of protein synthesis in isolated ribosomes using an amino-acid incorporating system	Norton and Kench, 1977

Table 2-1. SUBCELLULAR AND CELLULAR CADMIUM TOXICITY IN EXPERIMENTAL ANIMALS (CONTINUED)

Species	Cd Dose*	System(s) studied**	Effect(s) found**	Reference
Rat	--	Cyclic AMP and associated enzymes of tissue homogenates	Inhibition of both cyclic AMP phosphodiesterase and adenylate cyclase activity	Anthanson and Bloom, 1976
Turkey	Up to 0.7 mM	Adenylate Cyclase activity in erythrocyte membrane	Up to 100% inhibition (at 0.7 mM) of both forms of adenylate cyclase activity	Spiegel et al., 1976
Turkey; mouse; rabbit; guinea pig; dog; cat	1×10^{-4} M	Renal ATP-ase activity	Inhibition of renal Na+-K+ ATPase 10 times greater than Mg++ ATPase for all species tested	Nechay and Saunders, 1977
Rat	20 ppm in the preparations	Kidney, intestine, and salivary gland (homogenates) phosphatases	13 to 20% inhibition of acid phosphates in all preparations; 40% inhibition of alkaline phosphatase in salivary gland	Iqbal et al., 1976
Chick	2.5×10^{-5}M and greater	25-hydroxy-Vitamin D_3 metabolism	Complete inhibition of 1,25-dihydroxy-Vitamine D_3 at lowest level	Suda et al., 1974
Rat	0.5-3.0 μM	Liver mitochondria respiration	Uncoupling of oxidative phosphoratin; acceleration of State IV respiration	Kamata et al., 1976
Rabbit	Up to 3mM in medium for 20 hr.	Alveolar macrophages tissue culture	Reduction of cell viability; reduction of phophatase activity; disturbance in morphology (Cd 1 of 2 most toxic metals studied)	Waters and Gardner, 1975

Table 2-1. SUBCELLULAR AND CELLULAR CADMIUM TOXICITY IN EXPERIMENTAL ANIMALS (CONTINUED)

Species	Cd Dose*	System(s) studied**	Effect(s) found**	Reference
Mouse	4.3 mg/kg b.w. (LD_{50}) i.p.	Heterolysosome formation and function in kidney and liver	Inhibition (increasing over time) of proteolysis in liver particles 2 to 20 hr. after injection; less effect on kidney particles	Mego and Cain, 1975
Mouse	0.15 mg/kg b.w.; intragastric dose for 90 days	Catalase and carbonic anhydrase activity	Decrease in carbonic anhydrase activity in liver, kidney, and blood after 20 days; decrease in catalase activity after 60 days	Ogawa et al., 1973
Mouse	50 ppm in drinking water for up to 8 mo.	Subcellular localization of Cd	Localization of Cd mainly in apical vessicles, lysosomes, lysosomes, and proximal tubular cells	Popham and Webster, 1976
Rat	2.1 mg/kg b.w.; single injection with 115Cd tracer	Liver localization of Cd	Appearance of label in nucleus and cytoplasmic fractions; concentration of nuclear Cd higher in non-hostine protein	Hidalgo and Bryan, 1977
Rat	2 mg/kg/wk for 2 to 3 wk. by injection	Subcellular localization of Cd	Appearance of significant amounts in purified ribosomes and enzyme preparations	Norton and Kench, 1977
In Vitro Studies				
Rat	Various concentrations of Cd and other heavy metals	AHH of 10% liver homogenate	Marked inhibition of AHH complex with Cd most inhibitory of all ions studied	Tsang and Furst, 1976

Table 2-1. SUBCELLULAR AND CELLULAR CADMIUM TOXICITY IN EXPERIMENTAL ANIMALS (CONTINUED)

Species	Cd Dose*	System(s) studied**	Effect(s) found**	Reference
Mouse	About 4 mg/ml medium and higher	Alveolar macrophages, peritoneal macrophages, and polymorphonuclear neutrophils	Significant depression of respiratory burst when heat-killed *P. aeruginosa* added to medium	Loose *et al.*, 1977
Hamster	2.2×10^{-5} M	Phagocytic activity of alveolar macrophages	Significant reduction in phagocytic index (PI)	Graham *et al.*, 1975
C^3H-strain mouse	15.6 mg/ml medium	L-strain fibroblasts	Disappearance of ribosomes; changes in mitochondria including total destruction; swelling of endoplasmic reticulum	Kawahara *et al.*, 1975
Mouse	2.8 to 88.0 mM (0.3 to 9.4 mg/ml)	Subcutaneous connective-tissue L-cells	Reduction in cell viability; cellular LD_{50} 5.5 for exponential phase, 30.5 for stationary phase	Ozawa *et al.*, 1976

*Abbreviations: b.w.: body weight; i.p.: intraperitoneal injection; ppm: parts per million; --: information not available

**Abbreviations: AHH: aryl hydrocarbon hydroxylase; G-6-PD: glucose-6-phosphate dehydrogenase
Cyclic AMP: adenosine 3':5'-cyclic phosphate

that inhibition of the inducible enzyme complex aryl hydrocarbon hydroxylase (AHH) occurs in mice given 3-methylcholanthrene intraperitoneally (i.p.) in trioctanoin (0.01 ml/g) and cadmium ion in one of two injected doses: 5 mg/kg and 3 mg/kg. At the higher dose, enzymic activity was almost completely quenched, while little inhibition was noted at the lower exposure level. In a related in vitro study, using a 10 percent liver homogenate, Tsang and Furst (1976) showed marked inhibition of this enzyme complex by five different metal ions, of which cadmium was the most inhibitory.

An acute effect of cadmium on hepatic metabolizing enzymes in the rat was noted by Teare and coworkers (1977). A single i.p. injection of cadmium chloride at levels of either 2.5 or 3.8 mg/kg into male rats produced significant (25 to 60 percent) inhibition of aniline hydroxylase and nitroreductase activity and reduced microsomal P-450 content to about 50 percent of control values. These effects are not seen with o-demethylase activity. Complicating these observations is an apparent "buffer effect", the last-named enzyme showing some inhibition in phosphate buffer and more significant inhibition in Tris buffer.

Krasny and Holbrook (1977) assessed various parameters of drug metabolism in rats following a single i.p. dose of cadmium acetate (2.0 mg/kg). At 3 days post-exposure, hexobarbital-induced sleeping time was increased 24 percent while microsomal levels of cytochromes P-450 and b_5 were decreased by 44 percent and 27 percent, respectively. At day 7 these values returned to normal. The microsomal enzymes aminopyrine demethylase and aniline hydroxylase both showed inhibition: the former, 47 and 37 percent at days 3 and 7, and the latter, 32 and 23 percent at these same

time points. Heme oxygenase showed the greatest increase (350 percent of control) at 2 days post-injection, returning to normal at the end of 1 wk, while biliverdin reductase activity was not altered at any time.

Several reports have appeared describing the *in vivo* and *in vitro* effects of cadmium on adenylate cyclase and other components of cyclic AMP (adenosine 3':5'-cyclic phosphate) metabolism in animals.

Singhal and coworkers (1976) observed that, while chronic cadmium treatments in rats (daily i.p. injection of 0.25 or 1.0 mg/kg for 21 or 45 days) failed to alter AMP-phosphodiesterase activity, the amount of cyclic AMP and the activity of basal and fluoride-stimulated forms of hepatic adenylate cyclase were markedly increased. However, the amount of cyclic AMP binding to hepatic protein kinase was decreased, as was the kinase activity ratio.

In an *in vitro* study, Nathanson and Bloom (1976) have shown that both basal and hormone-stimulated adenylate cyclase activity of various tissue homogenates and their particulate fractions were inhibited by very low levels of cadmium and other heavy metal ions. Cadmium also inhibited cyclic AMP phosphodiesterase activity.

Using turkey erythrocyte membranes, Spiegal *et al*. (1976) showed cadmium inhibition of all forms of adenylate cyclase activity, with 100-percent inhibition at 0.7 millimolar (mM) concentration (78 μg/ml). Such effect could be offset by the use of mercaptoethanol and British anti-Lewisite (BAL), both metal chelants.

Nechay and Saunders (1977) studied the effects of cadmium on renal adenosinetriphosphatase (ATPase) preparations from various regions of kidney obtained from dog, cat, rat, rabbit, guinea pig, and mouse. At

cadmium levels of 10^{-4} M, Na^{+}-K^{+} ATPase was inhibited, regardless of source or type of enzyme preparation, with the effect being ten-fold greater than the corresponding inhibition of Mg^{++}-ATPase. The inhibitory effects were not altered by sodium or potassium levels, but were decreased by ethylenediaminetetraacetic acid (EDTA) addition.

Sugawara and Sugawara (1975) studied the effects of cadmium administration (100 ppm cadmium solution ad libitum for 30 days) on selected enzyme activity in duodenal mucosa in male Wistar rats. Inhibition of brush border ATPase and alkaline phosphatase and increase in the activities of isocitrate dehydrogenase and glucose-6-phosphate dehydrogenase (G-6-PD) were noted. Such in vivo effects could not be duplicated, however, with in vitro studies using comparable cadmium levels.

Iqbal et al. (1976) studied the in vitro effect of cadmium on phosphatases using homogenates of kidney, intestine, and salivary gland. Cadmium at 20 parts per million (ppm) inhibited acid phosphatases 13 to 20 percent in all these preparations, while significant inhibition of alkaline phosphatases (40 percent) at this level was seen only in a salivary gland preparations. Prior addition of zinc ion abolished the inhibitory effect of cadmium on alkaline phosphatase but had little effect on acid phosphatase.

Both in vitro and in vivo inhibition of succinic dehydrogenase and lactate dehydrogenase activity have been reported by Singh and Nath (1975). Injection of cadmium chloride (3.2 mg/kg) into rats caused 89 percent inhibition of succinic dehydrogenase activity using liver and testis preparations, but enhancement of lactate dehydrogenase activity. Both enzymes were inhibited on cadmium addition in vitro.

A number of studies have been concerned with the influence of Cd on biochemical activity in discrete subcellular components. Membranes, in particular, are especially vulnerable to the effects of cadmium and other heavy metals. They mediate the transer of materials in and out of cells via active transport and exchange mechanisms that require initial complexing. Such complexing may be easily interfered with by the surface binding of metals.

An organelle that is also quite sensitive to the effects of cadmium is the mitochondrion. Since all of the enzymatic machinery required for cellular oxidation, including oxidative phosphorylation, sugars, amino acids, and fatty acids are located in the mitochondria, there are potentially a number of sites within the mitochondrion where cadmium may impart an effect. According to Berry et al. (1974), the ion is active at three places.

(1) It binds to sulfhydryl groups of enzymes necessary for electron transport from the citric acid cycle to the electron transport chain.

(2) It inactivates one or more enzymes necessary for the synthesis of adenosinetriphosphate (ATP).

(3) It binds to ATPase, the enzyme required for the conversion of ATP, or adenosine diphosphate (ADP), an important energy source in cellular reactions.

In the study of Suda et al. (1974), kidney mitochondria were isolated from rachitic chicks, and their activity in tritiated 25-hydroxy-Vitamin D_3 (^3H-25-OH-D_3) metabolism was studied as a function of added cadmium ion. As little as 2.5×10^{-5} M cadmium ion completely inhibited the biosynthesis of the active form of Vitamin D_3. This is in contrast to in vivo studies in rats, where a Vitamin D-deficient diet also containing 300 ppm of

cadmium chloride for 3 wk furnished significant amounts of 1,25-dihydroxy-Vitamin D_3 (1,25-$(OH)_2$-D_3). These and other data led the authors to conclude that metallothionein (discussed below) serves as a protective factor against this aspect of cadmium toxicity.

Diamond and Kench (1974) studied liver mitochondria from rats chronically poisoned with cadmium (i.p. injection, twice weekly, 1 mg/kg/wk). Mitochondria exhibited diminished respiratory control with progressive cadmium intoxication. Cadmium added in vitro to mitochondria from exposed animals did not stimulate oxygen uptake, but control mitochondria respiring on succinate did show stimulation of oxygen utilization. While no pattern difference is seen between poisoned and control animals in reduced cytochromes, cadmium added in vitro at levels greater than or equal to 10^{-4} M prevented subsequent reduction of the cytochromes. This appears to be indicative of a cadmium effect prior to electron transfer through the cytochrome system.

Kamata et al. (1976) showed, in an in vitro study, that State III respiration with succinate in rat-liver mitochondria is strongly inhibited by cadmium. This inhibition is greater than for other heavy metals such as lead or mercury. At 0.5 to 3 micromolar cadmium, oxidative phosphorylation was decoupled, and State IV respiration was accelerated. In vivo, oral administration of cadmium (300 ppm in water) reduced the respiration control ratio and the P/O ratio but increased mitochondrial cytochrome a ($+a_3$) and cytochrome c ($+C_1$).

Stroll and coworkers (1976) have investigated the behavior of hepatic nuclei and microsomes from rats given cadmium chloride (0.34 to 3.4 mg Cd/kg, i.p.). When cadmium was added to isolated hepatic nuclei,

ribonucleic acid (RNA) synthesis was inhibited. When hepatic microsomes were preincubated to destroy messenger RNA (mRNA), the polyuridylic acid-directed incorporation of L-[^{14}C] phenylalanine was significantly inhibited by cadmium pretreatment; and such activity was inhibited in the same way when cadmium was added to preincubated microsomes from control animals.

In a related study by Norton and Kench (1977), cadmium administered to rats (2 mg Cd/kg/wk for 2 to 3 wk) caused inhibition of protein synthesis *in vitro* by isolated ribosomes in an amino acid-incorporating system.

Mego and Cain (1975) investigated the effect of cadmium on heterolysosome formation and function from the kidney and liver of mice. Pretreatment with cadmium inhibited proteolysis in liver particles 2 hr after i.p. injections of LD_{50} doses (4.3 mg Cd/kg), such inhibition becoming more pronounced up to 20 hr post-exposure. Kidney particles were less affected. Injections of cadmium also inhibited proteolysis of albumin in isolated liver heterolysosomes prepared 1 hr later.

Several studies have investigated the subcellular localization of cadmium. In one case, Popham and Webster (1976) employed a technique for the ultrastructural localization of cadmium in proximal tubule cells of mice consisting of precipitation of cadmium as the sulfide using ammonium sulfide after brief fixation in glutaraldehyde. In mice chronically exposed to cadmium (50 ppm in drinking water for up to 8 mo), cadmium was localized mainly in the apical vesicles, lysosomes, and cytoplasm of proximal tubular cells.

Hidalgo and Bryan (1977) used radioisotopic cadmium (^{115}Cd) to assess distribution of cadmium in rat liver after a single exposure (20 μ mol Cd/kg). The label was associated with the nucleus and the cytoplasmic

fractions. The nuclear cadmium was more concentrated in non-histone proteins than in the histone proteins. Cytoplasmic cadmium was associated with two metal-binding protein subfractions.

In the report of Norton and Kench (1977), significant quantities of cadmium were found in purified ribosomes and enzyme preparations when cadmium was given to rats (2 mg Cd/kg/wk for 2 to 3 wk).

The cytotoxicity of cadmium as seen in cell-culture studies has been reported by several investigators. In this regard, Waters et al. (1975) have employed an in vitro system for assessing the cytotoxic effect of cadmium and other heavy metals using rabbit alveolar macrophages exposed in tissue culture for 20 hr. Of the various toxic substances assessed, cadmium was one of the two most toxic at metal levels below 3 mM, with cadmium reducing cell viability without lysis. Cadmium also caused a reduction in the activity of acid phosphatase, a lysosomal indicator enzyme and an active component of alveolar macrophages, in a manner that parallels decreases in cellular viability. On the basis of parallel morphologic evidence, the following sequence of damaging events is suggested by the authors: (1) retraction of normally extended pseudopodia, (2) appearance of surface structures, (3) smoothing of the plasma membrane, and (4) effacement of cell architecture.

An in vitro technique has been developed to assess alveolar macrophage function specific for phagocytosis (Graham et al., 1975) and determine the effect of various metal ions, including cadmium. This entails a double-viability stain to eliminate non-functioning dead cells from phagocytic measurement. Cadmium, at a concentration of 2.2×10^{-5} M, showed significant lowering ($p < 0.001$) of the phagocytic index (PI)

Using pulmonary alveolar macrophages, peritoneal macrophages, and polymorphonuclear neutrophils from the mouse, Loose et al. (1977) observed no significant alteration in their resting oxygen consumption when incubated in media containing cadmium salts. When heat-killed P. aeruginosa were added to the cell suspension, however, a significant depression in respiratory burst following phagocytosis was apparent and dependent on cadmium concentration, starting at 3.6×10^{-5} M. According to the authors, impairment of phagocytosis by cadmium ion may be associated with the known inhibitory action of this toxin on the ATPases of myosin and cell membranes. Altered phagocytotic activity by these cells may explain the enhanced bacterial susceptibility posed by cadmium, as reported by Cook et al. (1975a,b).

An in vitro investigation by Kawahara et al. (1975) involved cells from L-strain fibroblasts derived from the C^3H-strain mouse, cultured with YLH medium and supplemented with 10 percent bovine serum. A level of cadmium ion of 15.6 μg/ml medium was used. Severe changes were noted under an electron microscope: ribosomal disappearance, mitochondrial changes from waning of membrane and irregular arrangement of cristae to total disintegration, and a swollen and bead-like endoplasmic reticulum. The organellar damage appeared to be much worse than that from mercuric chloride.

Ozawa et al. (1976) monitored the differential susceptibility of L cells in the exponential and stationary phases to cadmium ion. L cells derived from mouse subcutaneous connective tissue were grown in Ham's F12 medium supplemented with 15-percent calf serum, 50 U/ml Penicillin G, and 50 μg/ml streptomycin. Cadmium ion was added on the first, second, and fourth days (exponential phase) and the ninth, eleventh, and twenty-second

days (stationary phase) at a level to make a final concentration of 2.8 to 88.0 μM. The LD_{50} of cadmium ion for these cells in the two phases was 5.5 and 30.5 μM, respectively. Enhanced susceptibility in the exponential phase may be due to an increased cell membrane permeability. The corresponding cadmium contents of the cells in the two phases were 0.12 and 0.065 $\mu g/10^6$ cells.

2.3.2 Metallothionein

No discussion dealing with the subcellular metabolism and toxicity of cadmium would be complete without a consideration of the physiological role played by metallothionein. Metallothionein (the protein moiety thionein plus a complexed metal or metals) is a low-molecular-weight intracellular protein with a propensity for binding cadmium, zinc, mercury, copper, and to a lesser degree, certain other ions. It exists in at least two molecular forms. Structurally, cadmium binds to thionein through three sulfhydryl groups per metal atom, the sulfhydryl groups being available from the rather high cysteine content of the protein. While much in the way of metallothionein biochemistry has been reported, our interest is mainly centered on its function in the regulation of cadmium toxicity. An early review of metallothionein is presented in Friberg et al. (1974).

Cadmium-thionein and other metallothionein-like proteins have been isolated and studied from a number of organ systems of varous species, including man. Since metallothionein is an inducible protein, with its biosynthesis in liver and other organs being accelerated by challenging the organism with cadmium and certain other ions, much interest has centered on the role of metallothionein in mediating the movement and affecting the toxicity of cadmium.

While this protein may be involved in transport of cadmium in the blood, in organ distribution, and in excretion (Nordberg, 1972), questions have been raised as to whether metallothionein provides a protective function, as was first suggested by Piscator (1964), or whether this role is secondary to its regulation of zinc and/or copper metabolism.

In various experimental animals, pretreatment with a low dose of cadmium ion protects against a subsequent, usually fatal dose of the toxic agent (Parizek, 1957; Gunn et al., 1968), since with repeated doses a larger portion of the dose accumulates in liver and kidney as metallothionein (Webb, 1972).

In the study of Leber and Miya (1976), mice exhibited tolerance to cadmium toxicity after pretreatment with either cadmium or zinc acetate. Cadmium doses of 1.0 and 3.2 mg/kg given 2 days before cadmium challenge resulted in LD_{50} values of 6.0 and 8.2 mg/kg respectively, versus a value of 4.5 mg/kg without pretreatment. Similarly, the LD_{50} value is roughly doubled (6.5 mg/kg) when pretreatment with zinc is carried out 12, 30, and 48 hours before cadmium exposure. The amount of hepatic metallothionein was seen to be proportional to pretreatment dosing.

Webb and Verschoyle (1976) reported that pretreatment of female rats with a low dose of cadmium ion provided defense against a subsequent, usually lethal dose of the metal and also induced the synthesis of hepatic cadmium-thionein. While this protection was at optimum one to three days after pretreatment, both the increased content and increased biosynthesis of cadmium-thionein persisted beyond this time. Using radioisotopic cadmium (^{109}Cd), these workers also noted that, although cadmium ion is bound more strongly by the apoprotein, thionein, rats in which the levels of

zinc-thionein were elevated by starvation showed the same susceptibility to cadmium as animals on normal diet. This indicates that while synthesis of cadmium-thionein probably accounts for tolerance by animals of a larger quantity of cadmium given in multiple doses, Webb claims that neither preinduction of the protein nor zinc-thionein serves a protective function. This may be contrasted to the observation in the earlier study that zinc-thionein induced by zinc pretreatment does ameliorate lethality. As might be expected, accumulation of cadmium in the liver is greater under conditions of pretreatment, while uptake of the ion in other tissues (heart, spleen and pancreas) is unchanged.

In the related study of Probst et al. (1977), a dose-dependent tolerance to acute cadmium toxicity was evidenced by elevated LD_{50} values in cadmium-pretreated mice. Also, hepatic metallothionein levels increased with the increase in pretreatment dosing. Since pretreatment at a level of 2.0 mg Cd/kg, but not at 0.6 mg/kg or 0.2 mg/kg, resulted in elevated LD_{50} and cadmium-binding capacity relative to controls, it appears that a minimum dose of cadmium must be exceeded in order to occasion sufficient induction of metallothionein to modify the acute toxicity of the metal (Probst, 1977).

The protective behavior of cadmium pretreatment was also studied by Squibb and coworkers (1976), who observed that rats pretreated with 20 mg Cd/kg followed by another oral dose of 100 mg Cd/kg showed greater uptake of cadmium by liver, kidney, and testis. At all time points (1, 3 or 5 hr), liver cadmium was associated entirely with metallothionein. In animals not given pretreatment, metallothionein-bound cadmium was not observed

until 15 hr later. Radio-labeled cystein studies (^{35}S) showed that biosynthesis of the binding protein occurred following metal exposure. The observation that all of the cadmium in intestine was bound to metallothionein may suggest that the protein has a role in affecting cadmium absorption during low-level cadmium exposure.

Chen et al. (1975a) studied the synthesis and metabolic degradation of rat hepatic metallothionein stimulated by cadmium challenge. In regard to degradation of the protein, the half-life of 4.2 days observed after a single exposure to cadmium (subcutaneously, 26.7 μ mol/kg body weight) was not materially different from the value (4.9 days) observed after a second dosing, although liver cadmium content was doubled. Here, there is no stabilizing effect on the protein imparted by cadmium. Zinc, however, was lost from the metallothionein fraction at a rate similar to that of cystein [^{14}C]. Cadmium persisted in the liver-binding protein fraction up to 29 days post-injection and may do so in the face of observed protein breakdown by being released and immediately stimulating more thionein biosynthesis.

Cherian and Shaikh (1975) induced metallothionein in rats with cadmium, labeling the formed metalloprotein in vito with either ^{109}Cd, ^{14}C or ^{35}S. After isolation from liver and subsequent intravenous administration to rats (at Cd levels of 10, 30 and 200 μg Cd), it was observed that tissue distribution of the radiolabeled ion in the metalloprotein was different from that given as the chloride (200 μg Cd). When given as cadmium-thionein, the deposition of cadmium in kidney was higher than in liver and a significant urinary excretion of the ion was observed when given in that form. Furthermore, the distribution and excretion of the thionein moiety was similar to that of cadmium.

Several reports have since appeared in the literature relating the comparative toxicity of cadmium-thionein to ionic cadmium when administered as such. Cherian et al. (1976), for instance, isolated cadmium metallothionein from livers of metal-exposed rats, labelled the metalloprotein ^{109}Cd, and injected the material into a second group of rats. When compared with exposure to cadmium chloride, the organellar distribution of label from both forms in renal tubule cells was similar; but within 12 hours, degenerative changes were observed in the ultrastructure of renal tubule cells of animals dosed with the cadmium-thionein but not the cadmium salt. In a related study, Cherian et al. (1978) fed cadmium to mice in the form of either cadmium chloride or cadmium-metallothionein labeled with ^{109}Cd. The inorganic salt was accumulated in the liver, while protein-bound cadmium appeared in the kidney. The extent of absorption in both forms was similar. These data are significant in terms of exposure of human populations to cadmium in diet. In particular, food-animal organs such as liver and kidney, which are high in heat-stable metallothionein-bound cadmium, may provide an unacceptably high level of cadmium in terms of human renal burdens of the element.

Further evidence that cadmium-thionein is involved in the pathogenesis of renal tubular cell injury is the study of Nordberg and Nordberg (1975). Cadmium-metallothionein, labeled with ^{109}Cd in vitro, was injected into rats (1.6 μg Cd as either metalloprotein or $CdCl_2$). After 4 hr, over 80 percent of the injected dose was in the kidney when pure metallothionein was used.

Webb and Etienne (1977) observed that cadmium, when bound to thionein from either rabbit or rat liver, was 7 to 8 times more lethal to the rat

than was ionic cadmium. Zinc-thionein was not only nontoxic, however, but protected the animals from a subsequent, usually fatal dose of the cadmium-thionein. As also noted above, cadmium-thionein accumulated in the kidney; its lethality was associated with severe tubular damage. Other data in this study suggest that parenteral dosing with cadmium-thionein is followed by renal tubular uptake, and ensuing breakdown of the protein moiety liberates cadmium in the directly toxic ionic form.

In summary, the literature dealing with the cadmium-metallothionein relationship rather conclusively demonstrates that (1) with relatively acute exposure to cadmium, metallothionein serves a protective function for the organism, while (2) in the long-term chronic exposure situation, cadmium bound to metallothionein may be more systematically toxic than cadmium not bound to metallothionein.

2.4 RESPIRATORY EFFECTS OF CADMIUM

A number of acute and chronic respiratory effects of cadmium have been documented in man and animals. Friberg et al. reviewed the earlier literature in 1974.

2.4.1 Effects on Humans

In man, acute effects of cadmium via inhalation may not appear until some time after exposure, about 24 hours. Chief symptoms and signs are shortness of breath, general weakness, fever, and in extreme exposure cases, respiratory insufficiency with shock and death. These exposures are associated with pulmonary congestion and edema. Individuals surviving the exposure episode regain partial lung function but have a high probability of subsequently dying of chronic pulmonary insufficiency (Friberg et al., 1974). It has been estimated that the pulmonary retention of 4 mg in man is fatal (Gleason et al., 1969).

A recently reported case of fatal cadmium-fume pneumonitis (Patwardhan and Finckh, 1976) typifies the characteristics of the lethal form of acute cadmium intoxication. A welder spent the day welding handles to cadmium-plated drums. He went home at the end of the day showing no ill effects. Late that same evening, throat irritation developed and was followed by coughing, difficulty in breathing, fever and rigors. By the middle of the second day, he was severely dyspneic, cyanotic, febrile, and sweating. Impaired gait and speech were noted. Examination by X-ray showed heart enlargement, gross pulmonary edema, and elevated diaphragm. The patient expired about 3 days after exposure to occupational cadmium fumes. The lungs were voluminous, dark, congested and firm. Microscopic examination revealed degeneration; epithelial loss in bronchioles was present, and areas of regeneration were seen in which epithelial cells were spreading across the mucosal surface. Also present was diffuse congestion of alveolar capillaries with intra-alveolar proteinaceous exudate and shed alveolar lining cells and macrophages. Liver and lung cadmium values were 2.3 and 1.5 ppm, wet weight, respectively.

The chief pulmonary effect of chronic cadmium inhalation in man appears to be centrilobular emphysema and bronchitis arising after several years of occupational exposure to cadmium-oxide fumes, cadmium-oxide dust and cadmium-pigment dust (Friberg _et al._, 1974). Furthermore, lung impairment is likely at cadmium oxide fume levels below 0.1 mg/m^3.

With respect to populations at large, it should be noted that while the added body burden of cadmium contributed by cigarette smoking has been established, the role of cigarette cadmium in a cause/effect relationship to chronic pulmonary disorders, as distinct from smoking, _per se_, has yet to be demonstrated.

Several reports have appeared dealing with the effect of cadmium salts *in vivo* and *in vitro* on human alpha-1-antitrypsin, the major proteinase inhibitor in human plasma, a deficiency of which is associated with chronic obstructive lung disease. Chowdhurdy and Louria (1976) reported a concentration-dependent decrease in both antitrypsin level and inhibitory capacity in response to added cadmium. No other heavy metal was seen to have this effect. Glaser *et al*. (1977), however, claim that this effect is an artifact due at least in part to the acid content of the cadmium-dosing solution. Chowdhurdy and Louria (1977) in turn claim that a pH effect can only be part of the answer, since their *in vivo* work with mice indicates that a similar response occurs where pH is not a factor. A second report which is even more significant regarding the effect of cadmium on α_1-antitrypsin is that of Bernard *et al*. (1977). Their results, using workers exposed to excessive amounts of cadmium and showing signs of cadmium intoxication, did not indicate any reduction of α_1-antitrypsin in the blood of these workers.

2.4.2 Animal Studies

The acute effects of cadmium on the lung have been studied in experimental animals using generated cadmium fumes or cadmium aerosols. In one relevant study, mice exposed to cadmium fumes (1.3 to 1.7 mg/m^3) for 1 hr were studied by Fukase and Isomura (1976), who observed that such treatment caused increased content of glutathione as well as increased enzyme activities of the peroxidative metabolic pathway in the lung.

Yoshikawa and Homma (1974) assessed the 50-percent lethal concentration (LC_{50}) of cadmium fumes in rats using a particle size of 0.2 μ and found the value to be 25 mg/m^3 for a period of 30 min. Retention of

inhaled cadmium in the lung was 15 percent at a 30-min exposure level of 20 mg/m^3, and at 1 wk post-exposure 54 percent of the cadmium body burden was still retained in the lung.

Cadmium dust (1.1 mg/m^3 up to 4 wk) was seen by Watanabe et al. (1974a) to produce effects in rats that included septal interstitial pneumonitis and cell nuclear changes.

Hayes and coworkers (Strauss et al., 1976; Hayes et al., 1976) have carried out a series of inhalation studies in rats using a polydispersal cadmium chloride/saline aerosol. Using an aerosol of 0.1 percent cadmium chloride (4.5 μ, 10 mg Cd/m^3) for an exposure period of 2 hr, these workers (Strauss et al., 1976) found morphological evidence for acute lung injury by 24 hr post-inhalation. Examination by microscopy revealed multifocal damage in respiratory bronchioles. Ultrastructural studies showed:

(1) There was Type 1 cell edema with loss of plasma membranes by 24 hr.

(2) By the second day, the number of Type 2 cells had increased.

(3) By day 3, the damaged alveoli were lined by cuboidal cells.

(4) By day 10, these cells had regained the appearance of Type 1 cells.

In a related study (Hayes et al., 1976) assessing biochemical aspects of lung injury in rats using the above aerosol-exposure model, this same group noted that by the fourth day after exposure the total lipid content and lactate dehydrogenase and G-6-PD activities had all doubled, coinciding with doubling of lung weight and total lung DNA content. Malate dehydrogenase activity was very high 1 hr post-exposure, followed by subsequent reduction to a level comparable to the other enzymes. With the exception

of the effect on malate dehydrogenase, which is an index of mitochondrial injury, the biochemical responses appear to be nonspecific.

Adalis et al. (1977) studied the effect of cadmium on ciliary activity using isolated hamster tracheal rings and an organ-culture system. Statistically significant reductions in ciliary activity were seen at cadmium concentrations as low as 6 μM. Similarly, cilia from hamsters exposed to a cadmium chloride aerosol (2 μM, 2 hr, 50 to 1420 $\mu g/m^3$) were studied. In this case, the mean cilia-beating frequencies in all treatment groups were lower for recovery periods of 24 and 48 hr.

Gardner et al. (1977) have reported that cadmium inhalation (aerosol) also reduces the lung's ability to fend off microbial insults. Increase in mortality (15 to 70 percent) was observed in mice exposed to levels of 80 to 1600 $\mu g/m^3$ followed by streptococcal challenge. There was a marked decrease in the total number of alveolar macrophages recovered from lungs post-exposure, with a return to normal seen within 24 hr. Polymorphonuclear leucocytes increased dramatically by 24 hr after exposure, while lymphocyte numbers were unchanged. It is of interest to note the studies cited in the cytotoxicity section regarding the cell-culture studies of these same cells exposed to cadmium in a culture medium. Streptococci clearance from the lung was correlated with the mortality pattern.

Cadmium appears to affect the pulmonary tract even when the exposure is other than by inhalation. Miller et al. (1974) studied the effect of cadmium in rats exposed to dietary cadmium (17.2 μg/ml cadmium chloride; 6, 16 and 41 wk) in regard to the fine structure of connective tissue. After 6 wk of exposure, a general process of fibrosis was well established in sub-pleural tissue of the treated rats. Collagen fibrils were bundled.

There was increased density of the interstitial space merging into the basal lamina. An inflammatory response characterized by plasma cells and the deposition of the primary elements of fibrosis seem to be an early reaction to cadmium, progressing rapidly over a period of 16 wk, leaving the interstitium thickened at the lung periphery. The sub-pleural elastic layer showed focal disruption. Few polymorphonuclear leucocytes were seen. No abnormal fiber types were present after 16 wk of exposure. After 41 wk of exposure, there was a slow progression of the fibrosis. It is possible at least part of these effects are related to cadmium effects on copper metabolism via interference with copper enzymes (O'Dell et al., 1966; Murthy et al., 1972).

In the exposure study of Stelzner et al. (1975), intratracheal injection of 10 mM cadmium chloride resulted in degeneration of bronchial epithelium and widespread alterations in the lung. Regeneration of bronchial epithelium occurred by 8 wk, while the distal lung showed areas of emphysema and extensive scarring. Histochemically, there was a return by 8 wk to the normal pattern of staining for lysosomal enzymes. Ultrastructurally, rapid regeneration and ciliogenesis in bronchi and denuded basement membrane were seen, proceeding to hyperplastic Type II cells and layered membranous cells in the distal lung.

2.5 RENAL EFFECTS OF CADMIUM

The effects of both acute and chronic exposure to cadmium on the renal system have been noted in the literature from experimental animals and from clinical and epidemiological data. Both acute and chronic aspects of renal toxicity of cadmium have been reviewed by Friberg et al. (1974), Nordberg (1976), and Kawai (1976).

The most typical feature of chronic cadmium intoxication is renal damage, and thus, the kidney may be considered the critical organ in chronic exposure (Nordberg, 1976).

In particular, cadmium affects the reabsorption function of the proximal tubules, with an early sign of this effect being an increase in the urinary excretion of low-molecular-weight proteins--tubular proteinuria. The proteins, occurring in plasma, are normally almost totally reabsorbed, but the cadmium-injured kidney is less able to achieve complete resorption.

Later effects are aminoaciduria, glucosuria, and phosphaturia (Piscator, 1966a). Disturbances in kidney function are also manifested by effects on bone and mineral metabolism, via increased excretion of calcium and phosphorus. Early reports have described kidney stones in Swedish workers (Friberg, 1950) and osteomalacia in French workers (Nicand et al., 1942), as well as certain populations in Japan exposed to dietary cadmium (Friberg, et al. 1974). According to Piscator (1966a), once tubular proteinuria is seen, it is essentially irreversible.

2.5.1 Animal Studies

In experimental animals, the level of kidney damage due to chronic cadmium exposure is dose-related, from early-detected degenerative changes in the proximal tubules passing on to interstitial edema, glomerular capsule thickening, and basement membrane fibrosis as exposure continues. It is possible that renal vasculopathy accounts for the interstitial and fibrotic sequelae, while cadmium acting on the renal tubule directly may account for tubular changes (Kawai et al., 1976).

According to Kawai et al. (1976), there are morphologically distinct features of acute cadmium insult to the kidney in experimental animals in contrast to chronic exposure. In the acute case, hydropic swelling and acidophilic necrosis are seen, while tubular atrophy characterizes the chronic case. Pronounced edema in the surrounding interstitium is present, eventually resulting in interstitial fibrosis and nephrosclerosis at a later stage. Acute lesioning in tubular epithelium may be seen and is dose dependent. These observations suggest that vascular injury probably plays a major role in acute nephropathy.

In the studies of Kawai and coworkers (Kawai and Fukuda, 1974; Kawai et al., 1974) involving chronic cadmium poisoning in rats (10 to 200 ppm cadmium in tap water for 8.5 to 18 mo), tubular atrophy with interstitial edema was found in the kidneys of rats receiving 100 ppm cadmium or greater; and slight lesioning was observed in some animals at 50 ppm. The corresponding kidney metal levels were 150 and 37 μg/g wet weight, respectively. Cadmium excretion from kidney apparently increases as renal injury becomes more severe.

Itokawa et al. (1974) studied two groups of rats that received 50 μg Cd/g of diet with and without sufficient calcium for a period of 4 mo and observed considerable renal injury. The tubular epithelium was desquamated and vacuolized, and there was necrosis and partial hyalinization in glomerular capillaries with adhesions between the Bowman capsule and glomerular capillaries.

After 16 wk of feeding, Nomiyama (1975) observed that rabbits given 300 μg Cd/g in food began to show increased urinary amino acid excretion, concomitant with increases in certain enzymes. After 38 and 42 wk, total

protein and sugar levels respectively were elevated, but amino acid levels after 30 wk were similar for both control and exposed animals. The corresponding kidney cadmium levels for these time points were 200 and 300 μg Cd/g wet weight.

Axelsson and Piscator (1966) showed that in the rabbit proteinuria appeared before aminoaciduria. In man, proteinuria is certainly an earlier sign than aminoaciduria.

Suzuki (1974) found that, in rats exposed to low levels of cadmium for 16 wk, a kidney cortex level of 225 μg Cd was associated with proteinuria and a dramatic increase in urine cadmium.

Gonick et al. (1975), in their studies of cadmium-induced experimental Fanconi syndrome in female rats, gave repeated injections of cadmium ion (0.6 mg Cd/kg, i.p.) until the onset of glycosuria (24 days). By 2 days after the occurrence of glycosuria, the Fanconi syndrome was essentially complete in terms of: urinary volume increases; increased excretion of protein, glucose, and α-amino nitrogen; and increased fractional excretion of sodium, potassium, calcium, magnesium, and phosphate. Also, renal cortical Na^+-K^+-ATPase activity was reduced to less than half that of controls with reduction in ATP levels. The effect on this enzyme activity was consistent with ultrastructural evidence, i.e., extensive loss of basal membrane infoldings, the principal site of the enzyme's activity. Likewise, reduction in ATP levels paralleled evidence of alterations in the mitochondria.

Fowler et al. (1975) studied the effects of chronic cadmium administration on rat renal vasculature using low and normal calcium diets. Both diet groups of rats were exposed to cadmium via drinking water (0.2 to 200

ppm cadmium, 6 or 12 wk). Constriction of smaller renal arteries, mild dilation of larger arteries, and a diffuse scarring of peritubular capillaries were observed at 6 wk at even low doses (2 and 20 ppm Cd), with arterial constriction appearing to subside by week 12. These changes would indicate a decrease in effective renal circulation with time. While variation in calcium intake did not appear to influence the vascular effects studied, increased renal depositon of cadmium in the low-calcium rats was observed.

Since chronic cadmium exposure occasions renal tubular dysfunction, one might expect that this in turn would influence the metabolism of Vitamin D. In the section dealing with subcellular aspects, it was noted (Suda et al., 1974) that in vivo formation of 1,25-dihydroxy-vitamin D_3 was not markedly altered by a diet containing cadmium but that was Vitamin D deficient.

In the study of Lorentzon and Larsson (1977), however, in which rats were chronically exposed to cadmium in drinking water (0.22 and 0.69 m mole Cd/l) for a period of 3 mo and were on either normal or low-calcium diets, both levels of cadmium exposure led to reduced formation of 1,25-dihydroxy-Vitamin D_3 in kidneys as well as serum and liver, with the higher level yielding only minute amounts in the kidney. Even at the higher dose, there was only a slight effect on reduction of the conversion product with low calcium intake. Further, cadmium exposure showed a shift in Vitamin D metabolism over to formation of the less active metabolite 24,25-dihydroxy-cholecalciferol.

Pierce et al. (1977) investigated the use of urinary enzyme activities as markers for the nephrotoxicity of cadmium in the marmoset and rat.

Excretion of urinary enzymes in rats that had been dosed by subcutaneous (s.c.) injection (1.5 mg/kg/day) remained at control-animal levels to day 15. An increase of β-glucosidase activity occurred and continued to rise until the experiment was terminated ($p < 0.01$). N-acetyl-β-glucosaminidase activity increased by day 18. With marmosets, oral exposure to cadmium was without effect on urinary enzyme levels, but s.c. injection (6 days, 5 mg/kg/day) gave rise to an increase in enzyme activity by day 2 in the case of N-acetyl-β-glucosaminodase.

2.5.2 Human Studies

A number of studies have been directed to the chronic nephrotoxicity of cadmium in man, particularly cadmium workers and Japanese populations receiving environmental exposure via rice, fish, and water contamination. The earlier clinical and epidemiological studies have been reviewed by Friberg, et al. (1974).

Current investigations have included assessment of the extent and nature of the tabular derangement seen in man with chronic cadmium exposure, including the occurrence of proteinuria. In chronic cadmium poisoning in man, the urinary proteins vary in molecular weight from 10,000 to 200,000 with more than half of the total protein being smaller than albumin. The globulin fraction includes α_2-β_2- and α globulins, β_2-microglobulin, retinol-binding protein, and α-globulin L chains.

Several studies have been directed to characterizing the nature of urinary proteins excreted in excess in response to chronic cadmium exposure.

Peterson and Berggard (1971), for example, reported that retinol-binding protein (RBP) appears in human urine as a result of cadmium poisoning, and later investigators have studied the nature of the protein as well as its occurrence in other species in response to cadmium challenge.

Clark and coworkers (1975) in their studies of tritium-labeled retinol show that cadmium-treated rats excreted excess amounts of a protein bound to retinol or a retinol metabolite and having a molecular weight of about 4600.

Muto and coworkers (1976) exposed rabbits to cadmium (0.8 and 1.5 mg/kg body weight, s.c. 5 times per wk) and found a large excretion of retinol-bound protein of molecular weight 20,000. Though similar to human RBP (Kawai et al., 1971, 1972) they are immunologically distinct.

Perhaps a more significant urinary protein in terms of its being an index of renal damage induced by cadmium is β_2-microglobin. The biochemical and diagnostic aspects of this protein have been reviewed by Kjellström and Piscator (1977).

Piscator (1966b,c) found relatively high levels of the plasma protein β_2-microglobulin in the urine of cadmium workers, and Berggard and Beard (1968) subsequently isolated and characterized this protein from cadmium-worker urine.

In the normal kidney, reabsorption of β_2-microglobulin is essentially complete: 99.9 percent reabsorption (Johansson and Ravnkov, 1972; Evrin and Wibell, 1972). According to Evrin and Wibell (1972), 100 μg is excreted daily via the normal kidney.

Coupling of the known data regarding the renal biochemistry of β_2-microglobulin with its increased excretion in cadmium exposure indicates that levels of this protein are rather good indicators of tubular proteinuria induced by cadmium, and efforts have been made to evolve both good quantitative measurements of the protein and baseline levels for diagnostic purposes. Furthermore, the much higher relative increase in β_2-microglo-

bulin excretion than in total protein levels suggested that β_2-microglobulin analysis may be the most sensitive method of detecting the early stages of cadmium-induced renal tubular injury.

Of the various methods for quantitative assessment of this protein, the radioimmunoassay technique of Evrin et al. (1971) appears to be the most sensitive (2 μg/l), having a sensitivity about 50 times above that required for normal urine levels, about 100 μg. Details of the analysis have been reviewed (Kjellström and Piscator, 1977).

A number of epidemiological studies have been carried out using β_2-microglobulin measurement to assess proteinuria (Kjellström et al., 1977a,b; Kojima et al., 1977). The frequency distribution of individuals in normal groups was log-normal. Geometric average values of β_2-microglobulin in the general population range from about 50 to 100 μg/urine, while excretion levels in excess of 200 μg/l may be considered to be abnormal.

The dose-response relationship between increases in urinary excretion of this protein and cadmium exposure are evidenced by the data of Kojima et al. (1977) and Kjellström et al. (1977a).

In a number of cadmium-exposed areas in Japan, proteinuria has also been regarded as a manifestation of cadmium poisoning of the general population. These studies have been extensively reviewed and evaluated by Friberg et al. (1974) and by Shigematsu (1975), and particular attention has been given to Itai-Itai (Ouch-Ouch) disease, a condition embodying a number of toxic effects of cadmium and representing a classic case of environmental pollution in an industrialized society having severe consequences for the individuals involved. Itai-Itai disease is essentially cadmium-induced renal tubular dysfunction in a nutritionally-deficient

population, leading to osteomalacia and osteoporosis. Most of the victims were post-menopausal women who had given birth to several children and had a history of calcium and vitamin D deficiency.

Itai-Itai disease was first found in Fuchu in Toyama Prefecture where rice fields irrigated by the Jintsu River were contamininated by waste products from a mine. As cited by Friberg et al. (1974), proteinuria and glucosuria were more prevalent in the Itai-Itai disease belt than in a control area.

Presently, a large amount of data has been collected from parts of Japan other than Fuchu where cadmium exposure has been suspected. Methods of assessment of proteinuria vary in the study areas, however; and this may play a role in the fact that findings of different proteinuria studies are at variance with each other.

In many of the cadmium-polluted areas for which age-related prevalence of proteinuria was amenable to calculation (such as the areas of Fuchu and Tsushima), there is a substantial increase in prevalence with age; and in Fuchu the causal role of cadmium in this relationship is apparent. Furthermore, the population in many of the polluted areas showed enhancement of proteinuria with age which was significantly different with control populations.

In a recent report (Shiroishi et al., 1977) detailing the results of a joint Japanese-Swedish study of the nature of cadmium-induced renal changes in individuals with Itai-Itai disease, as assessed by β_2-microglobulin excretion, it was determined that proteinuria in Itai-Itai disease is tubular. In particular, β_2-microglobulin excretion, an index of tubular injury, was found to be over 100 times higher than in a reference population.

Epidemiological aspects of cadmium-polluted areas of Japan are discussed in a later section dealing with epidemiological studies.

2.6 THE CARDIOVASCULAR SYSTEM

This section will consider mainly the major aspect of cadmium's effect on the cardiovascular system: hypertension. A sizable body of data exists regarding the induction of hypertension in experimental animals in response to chronic cadmium exposure. While the cause/effect relationship of cadmium to experimentally induced hypertension appears to be well established, the issue of cadmium's role in the etiology of human hypertension still remains to be resolved.

2.6.1 Animal Studies

Perry (1976) and Friberg et al. (1974), have critically reviewed the earlier literature with regard to cadmium-induced hypertension in experimental animals such as the rat. The most relevant animal model for assessment of cadmium-induced hypertension is that employing oral exposure of the toxic element. Schroeder and Vinton (1962) first reported hypertension in animals fed cadmium, and this was confirmed by Perry and Erlanger (1971, 1974) and Sorenson et al. (1973).

Perry et al. (1977b) have recently reported that cadmium concentrations as low as 0.1 ppm in drinking water have induced the same degree of hypertension as the standard 5 ppm dose of cadmium; moreover, occasional subpopulations of "responders" have had a marked increase in pressure (Perry et al., 1978). In addition, simultaneous feeding of lead and cadmium can markedly augment cadmium-induced hypertension (Perry et al., 1977a).

The level of hypertension noted with chronic oral exposure, while statistically significant, is not great; and it is apparent from the literature that, in addition to a dosing regimen of a low cadmium level (5 ppm) in drinking water, other experimental details are important in observing the effect.

Frickenhaus et al. (1976) exposed rats to cadmium sulfide in their diets (26 mg Cd S/kg diet and 52 mg CdS/kg diet) for 3 mo, at which time no significant changes in blood pressure were seen, although the levels of cadmium ingested may have exceeded the lower exposure levels in the work described above. In this connection, Perry et al. (1977a) point out that hypertension in animals appears to be associated with a particular level of renal cadmium or a particular zinc-cadmium ratio, and that deviation in level up or down may cause the effect to disappear.

Parenteral adminstration of cadmium occasions acute hypertension in rats (Perry and Erlanger, 1971; Schroeder, 1967), rabbits (Thind et al., 1970), and dogs (Thind, 1973). While the hypertension caused by low-level cadmium feeding is moderate and permanent, hypertension from cadmium injection is transitory.

Thind (1974) studied blood-vessel wall characteristics in experimental hypertension induced by parenteral cadmium. Utilizing in vitro techniques, the vascular reactivity and elasticity of blood vessels from rabbits and dogs exposed to cadmium were measured. It was found that the vascular reactivity of rabbit aorta to angiotensin was significantly reduced in cadmium-treated animals, while hypertensive dog carotid artery was less responsive to angiotensin, norepinephrine, and serotonin. Furthermore, the hypertensive dog carotid artery developed significantly lower passive elasticity modulus.

In a related study, Thind and Fischer (1975) measured cadmium and zinc distribution in cardiovascular tissue of cadmium-treated and normal dogs. Cardiovascular tissue levels of cadmium in both groups were high in peripheral and smaller arteries and myocardium. The distal mesenteric artery, mesenteric artery branches, main renal artery, and coronary arteries, however, tended to accumulate cadmium while zinc levels were highest in the mesenteric artery branches. Kopp et al. (1978) using rats exposed to 5 ppm cadmium for 24 months found (a) depressed myocardial excitability, (b) decreased high energy phosphate in the heart, and (c) morphologic changes in cardiac muscle.

Thind (1973) found an approximately seven-fold increase in renin activity of generated angiotensin I following cadmium treatment in dogs. Perry and Erlanger (1973) reported an increase in plasma renin activity in cadmium-fed rats.

Porter et al. (1975), in studies of rats given cadmium, failed to find elevated blood pressure but noted that the treated animals evidenced decreased blood-pressure responses to norepinephrine, acetylcholine, isoproterenol, and atropine. Aortic strips from the animals also showed reduced reactivity to angiotensin, epinephrine, barium, and tyramine. These data suggested to the authors that production of hypertension and desensitization of vasculature to vasoconstrictors and vasodilators may be unrelated biological events.

The effects of low dietary cadmium on blood pressure and on sodium, potassium, and water retention in growing rats were investigated by Doyle et al. (1975). Sodium retention was greater in both male and female rats fed cadmium. There was a transitory greater retention or loss of potassium

in males and females, respectively, which abated by 330 days, although water retention was greater in treated animals at about the same time. No effect on blood pressure was seen, however. The absence of induced hypertension in this study was ascribed to differences in zinc in the diet, with zinc content being only a fraction of that used in the Perry and Schroeder models (vide supra) and other dietary differences as well.

2.6.2 Human Hypertension

As noted above, the case for cadmium as a factor in human hypertension is not clear-cut, and studies relating to this issue are discussed in the Human Epidemiology Section (4.).

2.7 EFFECTS OF CADMIUM ON REPRODUCTION AND DEVELOPMENT

An extensive literature documents cadmium effects on the gonads, associated organs, and other aspects of reproduction and development, as reviewed by Fleischer et al. (1974), Friberg et al. (1975), and NIOSH (1976). Many of the more dramatic effects reported, however, have been obtained with injections of the metal at relatively high dosage levels; this has led to questions about the environmental relevance of such findings. Other research has focused on: (1) mechanisms of action by which the toxic effects are exerted, (2) whether such effects occur at lower, environmentally encountered exposure levels and via relevant exposure routes, and (3) whether comparable effects occur in occupationally or environmentally exposed humans.

2.7.1 Testicular Effects

Induction of acute testicular necrosis by cadmium has attracted considerable attention in the literature on experimental animal models, but is of questionable relevance in assessing the impact of environmental cadmium

exposure on humans. In early studies (Parizek and Zahor, 1956; Parizek, 1957), a single subcutaneous (s.c.) injection of cadmium chloride at high doses (2.2 to 4.5 mg Cd/kg) was found to cause severe testicular damage in rats and mice. Within a few hours after cadmium injection, histologically detectable testicular changes such as interstitial edema occurred and progressed to extensive necrosis of the testes by 48 hr. Resorption of testicular tissue occurred by 10 days post-injection, and weights of accessory sex organs, seminal vesicles, and prostate glands were reduced. In a later study, Mason et al. (1964) injected a wider range of cadmium chloride doses (0.51 to 6.8 mg Cd/kg) s.c. into male rats and found the lowest effective dose to be 0.85 mg/kg.

The role of the testicular vasculature in determining cadmium effects on the testes has been one issue dealt with extensively in regard to characterizing mechanism(s) by which the metal damages male gonads. Much attention, for example, has been directed to whether cadmium-induced testicular necrosis results from a direct action of cadmium on the seminiferous tabule epithelium or occurs secondarily as a consequence of a primary damaging effect on the testicular vasculature. The case for the primacy of vascular damage has been well-argued in numerous individual research reports and several general review articles (e.g., Gunn and Gould, 1970; Friberg et al., 1975) and that view is the currently most widely accepted one in the field.

Arguments for the primacy of vascular effects underlying cadmium-induced testicular necrosis gained credence, in part, by virtue of variations in susceptibility of different species. It was first well-established that mammalian species possessing scrotal testicles were susceptible to the

effect, since virtually all such species tested show marked acute testicular necrosis following a single systemic injection of cadmium. Such susceptible species are listed in Table 2-2. In contrast, several non-scrotal species with abdominal testes, as listed in Table 2-2, appear to be resistant to the induction of testicular necrosis by cadmium. That factors beyond vascularization patterns are important, however, is suggested by: (1) demonstration of susceptibility among some non-scrotal species listed in Table 2-2, and (2) demonstration of variations in susceptibility between strains within the same scrotal species (Gunn et al., 1965; Taylor et al., 1973).

Other evidence supports the view that cadmium causes testicular necrosis via a primary effect on testicular vasculature. This includes ultrastructural studies demonstrating: (1) signs of cadmium-induced increases in vascular permeability in testes (Clegg and Carr, 1967), (2) evidence of pinocytotic activity in testicular capillary endothelial and perivascular cells as well as loosened endothelial desmosome junctional complexes and signs of microhemorrhaging (Berliner and Jones-Witters, 1975), and (3) changes in intratesticular capillary endothelial cell junctions leading to separation of endothelial cells (Fende and Niewenhuis, 1977). Also, Koskimies (1973) showed that serum protein increased in rete testis fluid within 10 min after cadmium injection, but not in seminiferous tubule fluid until 2 hr.

Additional studies have focused on biochemical mechanisms possibly underlying cadmium-induced testicular damage. For example, the activity of carbonic anhydrase (CAH), a zinc-containing metalloenzyme, was decreased in testes after cadmium administration; and inhibition of CAH was taken to be

Table 2-2. SPECIES VARIATIONS IN SUSCEPTIBILITY TO CADMIUM-INDUCED TESTICULAR NECROSIS

Species tested	Testicular damage susceptibility	Reference
Scrotal species		
Rat	(+)	Parizek (1957)
Rat	(+)	Mason *et al*. (1964)
Mouse	(+)	Parizek (1957)
Mouse	(+)	Gunn *et al*. (1965)
Guinea pig	(+)	Parizek (1960)
Rabbit	(+)	Kar and Das (1962)
Gerbil	(+)	Ramaswami and Kaul (1966)
Gerbil	(+)	Berliner and Jones-Witters (1975)
Hamster	(+)	Girod and Dubois (1976)
Dog	(+)	Chatterjee and Kar (1968)
Dog	(+)	Donnelly and Monty (1977)
Goat	(+)	Kar and Das (1962)
Monkey	(+)	Kar (1961)
Non-scrotal species		
Suncus	(-)	Dryden and McAllister (1970)
Fowls	(-)	Johnson *et al*. (1970)
Frog	(-)	Chiquoine (1964)
Toad	(-)	Biswas *et al*. (1976)
Toad	(+)	Chiquoine and Sunzeft (1965)
Doves	(+)	Maekawa *et al*. (1964)

Table 2-2. SPECIES VARIATIONS IN SUSCEPTIBILITY TO CADMIUM-INDUCED TESTICULAR NECROSIS (CONTINUED)

Species tested	Testicular damage susceptibility	Reference
Fish	(+)	Maekawa and Tsunenari (1967)
Fish	(+)	Sarkar and Mondal (1973)
Fish	(+)	Tafanelli (1972)
Brook trout	(+)	Sangalong and O'Hallran (1973)

important in the etiology of cadmium-induced testicular necrosis (Johnson and Walker, 1970). Subsequent work reported by Alsen et al. (1976), however, provides strong evidence against this. As for other research attempting to identify particular proteins as pathogenic targets for cadmium in the testes, that of Chen et al. (1974) revealed two cadmium-binding moieties corresponding to proteins of molecular weights (MW) of 10,000 and 30,000 in the soluble fraction of whole testes; and Chen and Ganther (1975) later provided evidence for involvement of the 30,000 MW protein in the pathogenesis of testicular necrosis. This, however, is not supported by the more recent data of Prohaska et al. (1977). Lastly, Omaye and Tappel (1975) demonstrated reductions in plasma and testicular glutathione (GTH) peroxidase activity that they hypothesized to be important in mediating cadmium-induced testicular necrosis.

Certain data suggest that some cadmium-induced degenerative changes might occur secondarily to damage androgen-producing (Leydig) cells of the testes. Such data include the demonstration after cadmium treatment of: (1) decreased plasma levels of androgens (Chandler et al., 1976; Saksena et al., 1977), and increased testicular cholesterol levels indicative of decreased androgen production by the testes (Dixit et al., 1975); (2) alterations of cyclic AMP metabolism in the primary and secondary reproductive organs of the male rat consistent with reductions in testosterone (Sutherland et al., 1974); (3) evidence of Leydig-cell necrosis or reductions in metabolic activities in those cells (Girod and Dubois, 1974, 1976; Dixit et al., 1975); (4) signs of hyperplasia of gonadotropic cells in the anterior pituitary (Girod and Dubois, 1974, 1976), as well as increases in plasma levels of leuteinizing hormone (LH) (Chandler et al., 1976) and (5)

autoradiographic localization of cadmium in testicular interstitial tissue (Nordberg and Nishiyama, 1972).

Chandler et al. (1976) observed changes in the ultrastructural integrity of the lateral prostate of the rat as early as one day after cadmium injections, too soon for decreases in circulating testosterone to have occurred. This suggests that cadmium may also exert a direct influence on the prostate before any further effects of reduced androgen levels are manifested. In addition Nordberg (1975) found that morphological changes in the seminal vesicles indicative of reduced testosterone levels occurred as a result of chronic exposures to doses of cadmium too low to produce alterations in testicular weight or histology, suggesting that cadmium can also exert effects on testosterone-producing testicular cells before necrosis occurs after vascular damage. Further support for this possibility is gained from another observation by Nordberg and Piscator (1972) on chronic cadmium doses below those producing testicular necrosis causing a significant decrease in the protein excretion of male mice before the onset of renal tubular dysfunction. Since the usual cadmium-induced proteinuria in mice was previously shown to be testosterone-dependent (Thung, 1956; Finlayson et al., 1965), the decreased production of testosterone was hypothesized as being an early effect of long-term cadmium exposure.

In view of the above results, much remains to be clarified concerning mechanisms by which acute high doses of cadmium cause testicular necrosis. Of greater importance here, however, is the issue of whether or not more chronic, lower-level exposures to cadmium cause significant morphological or functional changes in the testes.

Piscator and Axelsson (1970) reported that 0.5 mg Cd/kg doses of cadmium chloride, when administered subcutaneously to rabbits 5 times per week for 24 wk, caused no macroscopically or microscopically evident testicular changes but did cause marked kidney damage. In another study, Nordberg (1971) demonstrated that single, subcutaneous (s.c.) injections of cadmium chloride at 1 mg Cd/kg caused complete testicular necrosis in CBA mice, while single doses of 0.25 to 0.50 mg Cd/kg caused little or no damage to the testes. After administration of such doses 5 days/wk for 6 mo, no significant testicular changes were apparent at the 0.25 mg/kg dose level and only slight changes were evident at the 0.50 mg/kg level. This occurred despite the fact that testicular cadmium levels in these animals were 6 to 7 ppm, i.e., approximately 20 times as high as the levels (0.3 ppm) found to exist in the mice experiencing severe testicular necrosis after a single 1.0 mg Cd/kg injection. Repeated injections of 0.25 mg/kg doses, to stimulate metallothionein synthesis, prevented the induction of testicular necrosis by a 1.0 mg Cd/kg dose administered later. Also, no testicular necrosis occurred after injections of cadmium (1.1 mg Cd/kg) partially bound to metallothionein. When the same chronic dosage regimen as the first one used in the Nordberg (1971) study was employed in a subsequent experiment on renal effects, Nordberg and Piscator (1972) found that CBA mice receiving s.c. injections of 0.25 to 0.5 mg Cd/kg, 5 days/wk for 6 wk, developed signs of kidney damage.

Considered together, the above results appear to indicate that testicular damage does not occur after repeated administration of cadmium compounds at doses causing only slight or no kidney malfunction. Other data suggest, however, that more subtle testicular effects may occur in the

absence of clear-cut kidney damage. Nordberg and Piscator (1972), for example, found a significant decrease in protein excretion before the onset of renal tubular dysfunction resulting in marked proteinuria, and Nordberg (1975) demonstrated effects on the seminal vesicles in the absence of changes in testicular weight or histology after chronic cadmium dosing that produced little renal dysfunction. Thus, even in the absence of demonstrable morphological damage to the testes, biological changes suggestive of probable altered testicular function were detected at cadmium exposure levels below or equal to those producing signs of relatively slight renal damage.

In regard to dietary cadmium exposure, very low oral cadmium doses were reported to have been used as part of a joint Soviet-American project, as reported by Russian workers (Krasovskii et al., 1976). Chronic oral administration of cadmium chloride to adult male rats at four dose levels (control, 0.00005, 0.0005, and 0.005 mg Cd/kg) was achieved by cadmium concentrations of 0, 0.001, 0.01 and 0.1 mg/l, respectively, in the drinking water. At dose levels as low as 0.0005 mg/kg, numerous statistically significant gonadotoxic effects were reported to have occurred in conjunction with other, more general toxic effects. The Russian findings, which are difficult to evaluate adequately from their published description, must be viewed with caution, however, in view of unusually high blood cadmium levels reported for their control (70 μg Cd/l) and cadmium exposed animals (> 85 μg Cd/l) and in view of the cadmium doses used being far less than those likely to be present in food.

American phases of the same Soviet-American cooperative project have not yielded much evidence of testicular damage. Dixon et al. (1976) reported

that possible "subtle reproductive effects" of cadmium were assessed in male rats exposed orally to cadmium chloride at concentrations of 0, 0.001, 0.01, or 0.1 mg/l in the drinking water, yielding estimated maximum doses of 14 μg/kg/day. Randomly selected animals were taken for study after 30, 60 and 90 days of exposure. Using a variety of evaluations, no significant differences were observed between control and cadmium-exposed animals at any dose level or exposure time. Nor were any significant general toxic effects obtained with a variety of clinical serum chemistry tests.

In another study, Loeser and Lorde (1977a) reported that cadmium chloride fed to groups of 20 male and 20 female rats over a period of 3 mo in concentrations of 0, 1, 2, 3, 10, and 30 ppm caused no histopathological signs of damage in the gonads or any other organs. Similarly, no significant effects were observed after the administration of the same doses of cadmium chloride for 3 mo to groups of 2 male and 2 female beagle dogs each (Loeser and Lorke, 1977b).

The Loeser and Lorke (1977a,b) and Dixon et al. (1976) results raise serious questions about cadmium having significant effects on male reproductive organs or functions when administered chronically at low dose levels. Still, since little or no data were reported on tissue levels of cadmium achieved in those studies, it is difficult to place them in perspective in relation to cadmium exposures known to produce other types of damage, e.g., renal dysfunction. Also, it remains to be assessed as to whether longer periods of exposure at the dose levels used might not produce significant testicular effects.

2.7.2 Ovarian Effects

Stimulated in part by findings of testicular necrosis in rodents after exposure to high doses of cadmium, several early studies have analogously focused on the effects of high-dose cadmium exposures on the ovaries of female rodents. Kar and coworkers (1959) exposed female rats, 6 to 8 wk old, to cadmium chloride via subcutaneous injections of 10 mg Cd/kg and found some acute ovarian effects. More specifically, although ovarian and uterine weights were not significantly altered, the rate of follicular atresia was clearly affected. Medium- and large-sized follicles were initially damaged, as indicated by signs of atrophy among granulosa cells and ova, followed by complete destruction of follicles of all sizes by 48 hr postinjection. In addition, the normal response of the ovaries to exogenously administered gonadotropins was blocked, suggesting a possible interference of cadmium with actions of endogenous pituitary factors on the ovaries. In a later study, Kar et al. (1960) demonstrated that simultaneous injections of zinc or selenium along with cadmium prevented the ovarian damage otherwise obtained with cadmium alone. This is analogous to preventive effects of zinc and selenium against cadmium-induced testicular necrosis.

Evidence for cadmium-induced ovarian damage of the type described by Kar et al. (1959) has not been universally obtained by other workers. In that regard, Gunn et al. (1961) did not detect any pathological changes in the female reproductive tract or any other major organs in rats of another strain treated with 0.03 mM/kg of cadmium chloride; nor did Der et al. (1977b) observe any pathologic or abnormal histology of ovary or uterus after daily intramuscular injections of 50 or 250 μg $CdCl_2$ in adult Wistar female rats for 54 days, although persistent diestrus was seen in the 250

μg dose animals. On the other hand, very distinct gross and morphological correlates of antigonadal effects were observed by Kaul and Ramaswami (1970) in the female gerbil. After a single subcutaneous injection of either 0.22 mg Cd/kg in immature animals or 0.45 mg/kg in mature animals, considerable reductions in the weight of the oviduct in both the immature and adult female gerbils were seen, and histological examinations revealed widespread follicular atreasia and extensive ovarian hemorrhages. No evidence exists, however, for the induction of such ovarian damage by cadmium with lower-level exposure by inhalation or ingestion.

2.7.3 Embryotoxic and Teratogenic Effects

Considerably more information than that on effects of cadmium on the ovaries has been generated by the investigation of more general effects of cadmium on reproduction and early development. This includes studies on the embryotoxic and teratogenic effects of cadmium, as well as research on the transplacental transfer of the metal as a prenatal exposure route. Such studies indicate that both embryotoxic and teratogenic effects occur in many mammalian species after administration of high doses via systemic injection, but much less evidence has been advanced for such effects occurring at lower-level exposures via more environmentally relevant inhalation or oral exposure routes.

Early studies on the rat documented adverse effects of cadmium administration during pregnancy, including the demonstration of placental necrosis after high dose s.c. cadmium injections (Parizek, 1964) and heightened vulnerability of maternal animals themselves in terms of s.c. injections on day 21 of pregnancy causing hemorrhagic kidney necrosis and a 40-percent death rate among dams (Parizek _et al._, 1968).

In another study, Chernoff (1973) injected rats with cadmium chloride (2.5 to 7.5 mg Cd/kg) on each of 4 consecutive days, starting either on day 13, 14, 15, or 16 of pregnancy, and observed (1) a dose-dependent increase in fetal deaths, (2) decreased fetal weights, and (3) an increased rate of congenital anomalies (micrognathia, cleft palate, club foot, and small lungs). In contrast, Barr (1973) reported that cadmium chloride was not teratogenic when a dose of 16 μmole Cd/kg was injected s.c. into two different rat strains on gestation day 9, 10 or 11; but teratogenicity was observed for both strains after i.p. injections of the same doses of cadmium chloride, with marked differences between the stocks occurring in fetal mortality and incidence and types of malformations.

Studies on mice have provided further evidence for cadmium-induced embryotoxicity and teratogenicity in mammalian species. In one study, Yamamura (1972) reported that i.p. injections of 5 mg/kg of cadmium sulfate ($CdSO_4$) into pregnant mice from day 6 to 14 of gestation resulted in embryo deaths and congenital anomalies such as exencephaly, cleft palate, and bone malformations. Results obtained depended on the day of injection; that is, injections on gestation day 9 caused a low incidence of embryolethality (15 percent) and day 11 injections a high incidence of fetal death (87 percent) while injections of the same dose on day 12 produced a high lethality incidence (82 percent) but a low teratogenicity rate (5 percent). This pattern of results suggests possible differential sensitivity of fetuses or dams to various cadmium-induced effects depending upon gestation stage at which exposure occurs.

Other studies on mice have yielded information on dose-response relationships, including data suggesting a "no effect" level, and additional

evidence regarding genetic influences on the induction of fetal cadmium effects. For example, Ishizu et al. (1973) exposed pregnant mice on gestation day 7 to cadmium chloride via s.c. injections of doses of 0, 0.33, 0.63, 2.5, and 5 mg Cd/kg. Dose-dependent effects were observed at doses above a no-effect level of 0.33 mg/kg. This included dose-related increases in percentages of dead fetuses (9.7, 9.9, 11.9, 12.0 and 17.5 percent at the above respective doses) and increases in percentages of malformed fetuses found when sampled on day 18 of pregnancy (0, 0, 0.97, 19.5 and 59.0 percent, respectively). Consistent with findings discussed earlier, placental but not fetal concentrations of cadmium were detected, which reinforces the idea that the metal may not cross the placental barrier very well.

Evidence for genetically inherited differential susceptibility to cadmium-induced embryotoxicity has been provided by Wolkowski et al. (1974). Pregnant female mice of two different inbred strains were injected subcutaneously on different days of gestation. Mouse embryos and fetuses of one strain (NAW) were relatively resistant to death caused by maternal injections of cadmium, whereas embryos and fetuses of the other strain (C57BL) were relatively susceptible. Pierro and Haines (1976), have also reported findings confirming the relatively high susceptibility of the C57BL strain to embryotoxic effects of cadmium, and Eto et al. (1976) have shown A/Jax mice to be susceptible to increases in the incidence of cleft lip after i.p. injections of 5.9 mg/kd of $CdSO_4$ on day 10 of gestation.

The hamster is another species that has been shown to be vulnerable to cadmium-induced embryotoxicity and teratogenicity as indicated mainly by studies carried out by Ferm and coworkers. In one of their earliest studies

(Ferm and Carpenter, 1968), intravenous injections of cadmium in hamsters on day 8 of pregnancy were found to produce teratogenic effects, especially facial malformations such as cleft palate and lips. Further characterizations of teratogenic effects were carried out in subsequent studies (Mulvihill et al., 1970; Ferm, 1971; Gale and Ferm, 1973), with similar intravenous injections of $CdSO_4$ at a dose of 0.88 mg Cd/kg being used in each. Mulvihill et al. (1970), for example, presented evidence suggesting that the palatal clefts induced by cadmium in the golden hamster are likely due to mesodermal deficiencies in the palate region typified by defects in bone formation and delays in ossification. Other congenital malformations were reported by Ferm (1971) to occur in the hamster embryo, including limb defects such as amelia and phocomelia; and Gale and Ferm (1973) reported similar effects plus others following intravenous injections of 0.88 mg Cd/kg on gestation days 8 and 9, which correspond to the time of major organ differentiation in the hamster. Effects observed included malformations of the brain, eye, jaw, and tail as well as the fore and hindlimbs.

Several investigations by Ferm and coworkers have also provided information on protective effects against cadmium-induced fetal malformations. Ferm and Carpenter (1968) showed that the simultaneous injection of zinc with cadmium protects against the teratogenic effects of cadmium. In the same study, however, Ferm and Carpenter (1968) found that cobalt did not protect against cadmium-induced teratogenic effects, in contrast to the demonstration by Gabbiani et al. (1976b) of cobalt protection against the toxic effects of cadmium on sensory ganglia and testes. Subsequent research indicated that the protective effect of zinc was not simply due to that metal's influence on the transplacental transfer of cadmium (Ferm et al.,

1969). Overall, these results were interpreted by Ferm (1971) as indicating that cadmium may act directly on embryonic tissue by interfering with zinc-metalloenzymes such as carbonic anhydrase or alkaline phosphatase. By anology, possible interactions of cadmium with selenium-dependent enzymes may also be indicated in view of protection being offered against teratogenic effects of cadmium by selenium administered within 30 minutes of an injection of an otherwise teratogenic dose of cadmium. Also, Semba et al. (1974) demonstrated that pretreatment with low doses of cadmium before injections of high doses of the metal protects against high-dose cadmium teratogenic effects such as exencephaly. In view of these latter results, a possible induction of a protective metallothionein protein might be hypothesized to explain the protective effects of zinc and other metals against cadmium's teratogenic effects.

It should be noted that not all heavy metals exert beneficial effects when administered with cadmium. Thus, although simultaneous injections of cadmium and inorganic lead salts in the pregnant hamster yielded protective effects against typical teratogenic effects of cadmium, such combined injections apparently potentiated characteristic teratogenic effects of lead. They also induced some effects, e.g., severe malformations of the lower extremities and umbilical hernias, not usually seen after the injection of either metal alone (Ferm and Carpenter, 1968). Similarly, additive embryotoxic effects are seen if cadmium is injected along with mercury (Gale, 1973).

The above studies utilized acute or subacute systemic injections of relatively high doses of cadmium; questions can therefore be raised about the relevance of the observed fetotoxic and teratogenic effects for the

assessment of potential effects in humans typically exposed via different routes (oral and inhalation) and to much lower levels of cadmium. Of more importance for present purposes, then, are animal studies which have employed inhalation or oral exposure routes for the administration of low levels of cadmium on a more chronic basis. The papers to be considered are those by Cvetkova (1970), Schroeder and Mitchener (1971), Pound and Walker (1975), Wills et al. (1976), Choudhury et al. (1977), and Campbell and Mills (1974).

In the Cvetkova (1970) study, female rats were exposed for up to 7 mo to $CdSO_4$ (3 mg/m^3) via inhalation. Alterations in the estrous cycle were observed in 50 percent of the exposed rats by 2 mo and in 75 percent by 4 mo, before mating was carried out. Upon sacrifice of half of the pregnant dams on gestation day 22, no significant effects on fetal mortality were found, nor was evidence obtained for prenatal teratogenic effects of cadmium. The remaining control and exposed mothers delivered litters of comparable sizes, but the offspring of the exposed mothers were smaller, weighed less than those in control litters, and experienced a higher perinatal mortality rate.

Evidence for teratogenicity of orally administered cadmium was reported by Schroeder and Mitchener (1971). They exposed mice to cadmium in the drinking water at doses of 10 μg Cd/ml continuously throughout a sequence of breeding of randomly selected pairs of males and females over a 6-mo exposure period. Males and females randomly selected from among the F_1 generation litters were similarly allowed to breed ad libitum, as were pairs from the succeeding F_2 generation. Control animals not exposed to cadmium were bred in a similar manner. The results indicated that orally administered cadmium was quite toxic to breeding mice, with some congenital

anomalies such as sharp angulation of the tail being seen in exposed F_1 and F_2 generation offspring as well as increased mortality before weaning and reduced rates of growth. The experiment was discontinued when 3 of 5 exposed F_2 generation pairs failed to breed.

Pond and Walker (1975) assessed the effects on reproduction of 200 ppm of Cd as $CdCl_2$ added to diets varying in calcium content (0.07 percent and 0.96 percent calcium). Although numbers of live or stillborn pups per litter were not significantly altered and no gross anomalies were seen, high cadmium content in the diet did significantly reduce pup birth weight. Concentrations of cadmium in the bodies of pups were doubled in the low-calcium groups when compared to the high-calcium dosed animals.

Wills et al. (1976) evaluated the effects of orally administered cadmium on both rats and monkeys. Both male and female rats were exposed via feed containing 33 or 73 ppb of cadmium chloride, and monogamous matings were allowed until four litters per couple were produced. Exposure at 33 or 73 ppb of cadmium via the feed continued for the offspring, which were also mated, as were successive generations until four generations had been produced. There was a slight increase in fertility among the 73 ppb exposure group animals but not in the 33 ppb group. Body-weight gain deficits were observed at both exposure levels, but no significant macroscopic or microscopic changes were found in the 286 rats assessed that could be attributed to the cadmium exposures. Rather, relatively minor changes observed were thought to be due to spontaneous disease, including tumors of similar types found in control and both cadmium-exposure groups. The lack of striking morphological changes might be expected, however, in view of the very low, almost trace amounts of cadmium used (which were below levels normally seen in most rat chows).

The same authors (Wills et al., 1976) also fed four female monkeys cadmium chloride in a sweetened beverage at 1.5 or 3.0 μg/kg/day, with a fifth monkey serving as a nonexposed control. Unfortunately, the control monkey and one exposed at 1.5 μg/kg died after 6 months from disease processes apparently unrelated to the cadmium exposure. The other females, which survived 18 months of cadmium exposure, were mated with nonexposed males; one at each dose level became pregnant and each later delivered a single infant, the lower-dose animal prematurely. No congenital anomalies were seen, and both infants appeared to nurse and develop normally. These results do not suggest that the cadmium exposure used had any major effects. They are, however, of very limited value due to the very small numbers of animals tested.

While the results of Wills et al. (1976) on monkeys are of very questionable import, the findings obtained in the other studies on rats and mice do appear to have some value for the analysis of the effects of chronic low-level cadmium exposures on reproduction and development. In at least one study (Schroeder and Mitchener, 1971), for example, significant teratogenic effects were found, but with the anomalies seen after long-term oral exposure being different from those reported in earlier studies to be induced by acute, high-level exposure via systemic injections. Another, much more consistent effect reported in several of the studies, however, is that of reduced birth weights and/or deficits in postnatal body weight gain for the offspring of rats or mice chronically exposed to cadmium. One crucial question, then, concerns the etiological bases underlying the observed body weight deficits, i.e., are they due to direct effects of cadmium on the fetus resulting from transplacental transfer of the metal or

do such deficits occur secondarily as the result of other cadmium effects, including possible actions on mothers of affected offspring? A number of studies have generated results bearing on this issue and, in general, appear to indicate that transplacental transfer of the metal probably plays a far less important role than other factors.

Many studies indicate that transplacental transfer of cadmium does not occur to any great degree. Ishizu et al. (1973), for example, reported on pregnant mice which were given s.c. injections of 2.5 mg Cd/kg as cadmium chloride on day 7 of pregnancy. Cadmium concentrations were about 10 times higher in the placentas of the cadmium-exposed animals than in controls, but the fetal concentrations were similar in each group (about 0.03 μg/g) although the levels in the liver and placenta of exposed mothers were 17 μg/g and 0.19 μg/g, respectively.

The Ishizu et al. (1973) results are consistent with findings of little fetal uptake during late gestation as assessed by autoradiography (Berlin and Ullberg, 1963). They also comport well with other results. Specifically, Ferm et al. (1969) showed that only small amounts of radioactive cadmium reached the fetus on the eight to ninth day of gestation in the hamster, while Wolkowski (1974) found that trace amounts of ^{109}Cd corssed into the fetus on days 13 and 17 of gestation in mice and Lucis et al. (1971) reported that only low amounts of cadmium crossed the placenta during the first third of gestation in the rat.

More specific characterization of parameters associated with transplacental transfer of cadmium in animals has been attempted, both by autoradiography (Dencker, 1975) and biochemical evaluations (Sonawane et al., 1975). In the Dencker study, pregnant hamsters and mice were injected

intravenously with 20 μCi $^{109}CdCl_2$ (i.e., 0.21 μg ^{109}Cd) at different times during pregnancy. Then, the whole animal, the uterus, or the embryos were processed for autoradiography. On the eighth day of gestation, low amounts of cadmium accumulated in the gut of embryos of both species. None, however, was found in the embryos with injection beyond the ninth day (hamster) or the eleventh day (mouse).

In the Sonawane et al. (1975) study, placental transfer rates of cadmium in rats were assessed in relation to dose (0.1, 0.4 and 1.6 mg Cd/kg) and gestational age (12, 15 and 20 days) at which pregnant dams were injected intravenously with a single dose of $^{109}CdCl_2$ (approximately 20 μCi/animal). The animals were sacrificed 24 hr after injection of the tracer, and ^{109}Cd concentrations were measured in the fetus, placenta, maternal liver, and blood. As shown in Table 2-3, very small amounts of cadmium were found to cross the placenta at each dose and gestation age, with increasing amounts accumulating in the fetus as a function of increasing dose and gestational age. Also, placental to maternal blood cadmium concentration ratios increased with gestational age but not with dose (Table 2-4), and placental to fetal cadmium concentration ratios decreased in reverse relationship to increasing dose and age, as shown in Table 2-5. These results contrast with some of those described above, which suggested that some early cadmium crossing of the placental barrier occurs, but not late in pregnancy. In either case, it appears that only a very small amount of transplacental transfer of the metal occurs in experimental animals during pregnancy.

As for transplacental transfer of cadmium in humans, only barely detectable levels have been reported to exist in human fetuses at various

Table 2-3. CADMIUM IN PLACENTAS AND FETUSES[a]

	Dose, mg/kg	Cd, %/g of injected dose[b] Gestation day 12	Gestation day 15	Gestation day 20
Placentas[e]	0.1	0.063 ± 0.043 (1.6)	0.0115 ± 0.49 (5.8)	1.403 ± 0.293 (5.6)
	0.4	0.232 ± 0.032[c] (1.6)	0.142 ± 0.124[d] (4.7)	1.347 ± 0.127 (5.8)
	1.6	0.206 ± 0.057[c] (1.3)	0.466 ± 0.147[d] (3.8)	0.587 ± 0.167 (6.9)
Fetuses[f]	0.1	0.00012 ± 0.00004 (1.1)	0.0014 ± 0.0001 (6.8)	0.0019 ± 0.0003 (64.7)
	0.4	0.0022 ± 0.0023[d] (1.1)	0.0027 ± 0.001[d] (7.6)	0.0036 ± 0.0016[d] (69.1)
	1.6	0.0217 ± 0.0111[d] (0.9)	0.0096 ± 0.0026[d] (4.9)	0.0152 ± 0.0058[d] (50.8)

[a]From Sonawane et al., 1975; rats sacrificed 24 hr after Cd treatment at various dose levels.

[b]Numbers in parentheses indicates average weight of placentas per litter or average fetal weight per litter. At least three animals were used to obtain each value.

[c]Significantly different from 0.1 mg/kg dose level, $p < 0.05$.

[d]Significantly different from 0.1 mg/kg dose level, $p < 0.01$.

[e]The dose-response test for placental data revealed significant dose-response relationships for day 12 and day 15 groups significant gestational day relationships at the 0.1 and 1.6 doses at least at $p < 0.05$.

[f]The dose-response test for fetal data revealed significant dose-response relationships for all gestational groups and gestational day differences at the 0.1 dose at least at $p < 0.01$.

Table 2-4. PLACENTAL TO MATERNAL BLOOD CONCENTRATION RATIOS[a]

Dose, mg/kg	Ratio placental: maternal blood Cd		
	Gestation day 12	Gestation day 15	Gestation day 20
0.1	14.9 ± 3.0	37.9 ± 7.8	118.8 ± 47.7[b,c]
0.4	12.3 ± 6.4	26.8 ± 4.5	58.7 ± 17.2[b,c]
1.6	11.8 ± 7.9	25.9 ± 8.8	52.5 ± 36.3[b,c]

[a]From Sonawane et al., 1975.

[b]The dose-response test revealed significant gestational day differences for all doses at least at $p < 0.05$.

[c]Significantly different from the 12th day treatment, $p < 0.01$.

Table 2-5. PLACENTAL TO FETAL CADMIUM CONCENTRATION RATIOS[a]

Dose, mg/kg per day	Ratio placental: fetal Cd		
	Gestation day 12	Gestation day 15	Gestation day 20
0.1[c]	618.00 ± 409.11	103.94 ± 29.28	78.877 ± 32.248
0.4	266.11 ± 232.92[b]	55.92 ± 17.41	41.852 ± 16.786[b]
1.6	11.23 ± 4.16[b]	56.64 ± 7.56	42.690 ± 2.244[b]

[a]From Sonawane et al., 1974; ratios are based on percentage of injected dose/g found in placentas and fetuses.

[b]Significantly different from 0.1 mg/kg dose level, $p < 0.01$.

[c]The dose-response test revealed significant dose-response relationships for the day 12 and day 15 groups at least at $p < 0.01$.

gestation stages based on analysis of autopsy materials (Chaube, 1973). Further confirmation of this applying to humans is provided by the work of Baglan et al. (1974) demonstrating only relatively small amounts of cadmium in freshly obtained human placentas, umbilical cord blood, and fetuses.

Given that only very small amounts of cadmium cross the placenta and accumulate in the fetus based on the above data, other factors are probably crucial in mediating cadmium effects on fetal and neonatal growth and development. Among such factors implicated as likely being important are effects of cadmium on maternal and fetal levels of essential elements such as zinc and copper. Maternal zinc deficiency has been shown to cause fetal abnormalities in experimental animals (Hurley and Swenerton, 1966; Hurley et al., 1971), and it would not be surprising if well-known effects of cadmium on zinc distribution were exacerbated in pregnant animals in a manner so as to induce fetal abnormalities secondary to a maternal or fetal zinc deficiency. Consistent with this, Pond and Walker (1975) and Choudhury et al. (1977) have reported lowered zinc concentrations and decreases in birth weight in pups of rats orally exposed to cadmium during gestation either at 200 mg/kg of cadmium in the diet or at 17.4 mg/l of cadmium in the drinking water, respectively. The results of the Choudhury et al. (1977) study are summarized in Table 2-6. Interestingly, no increase in fetal cadmium accompanied decreases in fetal zinc and other elements in the Choudhury et al. study, suggesting that such effects were likely secondary to cadmium influences on maternal nutritional state rather than directly on the fetuses.

Table 2-6. EFFECT OF MATERNAL DIETARY CADMIUM (17.2 μg/ml), GIVEN DURING GESTATION, ON BODY WEIGHTS AND BODY TRACE METALS OF NEONATES[a]

Experimental group	Birth weight (g)	Lactation wt. gain (g)	Zinc	Copper (μg/g pup dry weight)	Iron	Cadmium
Control	6.8 ± 0.1	52 ± 1.0	116 ± 4	9.4 ± 0.4	330 ± 6	0.46 ± 0.05
Cadmium	6.4 ± 0.1*	44 ± 1.6	104 ± 3*	5.7 ± 0.4**	267 ± 17**	0.48 ± 0.04

[a]From Choudhury, et al., 1977.

Data expressed as means ± SEM. Statistically significant difference, Student "t" test.

* $p < 0.05$.

** $p < 0.01$.

to cadmium influences on maternal nutritional state rather than directly on the fetuses.

In both the Choudhury et al. (1977) and the Pond and Walker (1975) study, fetal copper as well as zinc levels were reduced by cadmium exposure during pregnancy, and iron levels were also significantly reduced in the Choudhury et al. study. Consistent with the findings on copper reductions in fetal rats, Anke et al. (1970) have reported a trend toward reduced copper levels in newborn lambs after cadmium exposure of maternal ewes during pregnancy. Fetal concentrations of cadmium, however, were not increased, again suggesting that the fetal effects were secondary to effects on the maternal animal or cadmium inhibition of transplacental transfer of copper.

Persisting effects of cadmium exposure during pregnancy on the postnatal development and growth of offspring have also been demonstrated. For example, Choudhury et al. (1977) reported that the neonates experiencing the above types of essential element deficiencies, which were weaned without access to cadmium except that contained in the mother's milk during suckling, were later found to exhibit significantly depressed spontaneous activity and other neurobehavioral deficits in the absence of any overt teratogenic effects. Similarly, deficits in growth, plasma copper concentrations, and cytochrome oxidase activities have been reported for lambs born to ewes exposed to 3 mg/kg of cadmium in the diet (Bremner and Campbell, 1978).

2.8 ENDOCRINE EFFECTS OF CADMIUM

Only limited information exists on possible endocrine effects exerted by cadmium, with most studies bearing on this issue having employed relatively high doses of cadmium often given by injections rather than lower

doses administered orally or by inhalation. Still, a variety of endocrine effects have been demonstrated, and some of the more salient findings are reviewed below.

2.8.1 Gonadal Effects

Extensive evidence documents the effects of cadmium on the gonads, especially the testes, as was reviewed in some detail under the earlier Reproduction and Development section (2.7). As reviewed there, severe testicular necrosis has been well established as being one of the more notable consequences of high-level cadmium exposure, and that necrosis has been shown to involve endocrine cells within the testes as well as the testicular vasculature and germinal epithelium. In fact, some evidence was cited which suggests that damage to the endocrine (Leydig) cells of the testes may occur at cadmium-exposure levels below those producing initial signs of significant kidney damage (i.e., proteinuria). At high dose levels, consequently altered testosterone productions may contribute to deterioration of testicular germinal epithelium and other androgen-dependent tissues. In contrast, as also reviewed earlier, relatively little evidence has been advanced for cadmium effects on female gonads.

2.8.2 Pancreatic Effects

High accumulation of cadmium in the pancreas of humans and animals has been reported in several studies of cadmium poisoning (Friberg, 1957; Smith et al., 1960; Barbieri et al., 1961; Ishizaki et al., 1970; Nordberg and Nishiyama, 1972), as has altered pancreatic excretory function in Itai-Itai patients (Murata et al., 1970). This suggests that the metal may affect the pancreas, and cadmium effects on carbohydrate metabolism have been hypothesized as being due to cadmium-induced damage to the pancreas.

In regard to the induction of hyperglycemia by cadmium, reported to occur in rabbits (Voinar, 1962), dogs (Caujolle et al., 1964) and mice (Ghafghazi and Mennear, 1973), evidence has been advanced for that effect being mediated mainly through the adrenals rather than the pancreas (Ghafghazi and Mennear, 1973). Reductions in glucose tolerance induced by cadmium, however, have been linked to cadmium-induced alterations in pancreatic function. Evidence supporting the possibility of cadmium-induced effects on pancreatic secretory activity include: (1) the finding that cadmium accumulated equally in endocrine and exocrine parts of the pancreas (Friberg and Odeblad, 1957), and (2) the demonstration of decreases in the ratio of pancreatic beta to alpha cells in the rabbit after cadmium treatment (Barbieri et al., 1961), and (3) reports of observed decreases in concentrations of circulating insulin in mice after a single cadmium injection (Ghafghazi and Mennear, 1973). In addition, Ithakissios et al. (1975) treated rats every other day for 70 days by injections of cadmium acetate solution at 0.25 to 0.50 mg Cd/kg i.p. and found decreased insulin secretion at the 0.50 mg/kg dose.

That glucose tolerance may be impaired through cadmium reducing the insulin secretion of the pancreas, has been implicated more directly through the demonstration of Ghafghazi and Mennear (1975) of cadmium inhibition of insulin secretion by the isolated perfused rat pancreas in response to glucose challenge. The latter authors hypothesize that the effect is most likely due to interference by cadmium with calcium uptake by the pancreatic beta cell.

Possible protective effects of various substances against the pancreotoxic effects of cadmium have also been investigated. For example, Merali

and Singhal (1975) reported that administration of selenium concurrently with cadmium ameliorated cadmium-induced hyperglycemia, hypoinsulinemia, glucose intolerance, and suppression of pancreatic secretory activity. Also, Ghafghazi and Mennear (1973) found that repeated administrations of cadmium did not produce the significant reduction in pancreatic insulin secretion seen after a single larger injection of the metal, and Yau and Mennear (1973) obtained results suggesting that a pancreatic metallothienin protein is produced in response to cadmium.

2.8.3 Adrenal Effects

The possible involvement of the adrenals in the mediation of cadmium effects on other organ systems has been suggested by several studies. For example, Ray and Chatterjee (1973) found that reserpine and adrenalectomy blocked certain cadmium-induced effects on the testicles, and they hypothesized that adrenal catecholamines (CA's) may be important in mediating cadmium effects on the testes, perhaps by affecting testicular blood flow. Also, evidence has been advanced for the induction of hyperglycemia by cadmium being mediated through effects on the adrenals, since adrenalectomy abolished the hyperglycemic response of mice to cadmium (Ghafghazi and Mennear, 1973).

More direct evidence for cadmium affecting the adrenals has been generated. For example, Hart and Borowitz (1974) demonstrated that cadmium was moderately effective in causing prolonged release of CA *in vitro*, possibly through interactions with intracellular calcium in adrenal medullary cells. In a follow-up study, Leslie and Borowitz (1975) obtained data interpreted as indicating that not only can cadmium initiate catecholamine secretion from the adrenal medulla, but it also appears to

interfere with calcium removal from adrenal medullary cells, thereby inhibiting termination of the secretory response.

Additional data consistent with the above have been obtained in an in vivo study by Rastogi and Singhal (1975). Adolescent male rats were injected i.p. daily with cadmium chloride at doses of 0, 0.25, or 1.0 mg/kg for either 21 or 45 days. The results showed that daily treatment with either 0.25 or 1.0 mg/kg of cadmium for 21 days significantly increased adrenal weights, but such weights were still increased after 45 days of exposure only in the 1.0 mg/kg group. On the other hand, treatment at either dose level resulted not only in significantly enhanced CA levels after 21 days but also in even more marked increases in CA levels by 45 days and significant increases in tyrosine hydroxylase (TH) activity in the 1.0 mg/kg group after 45 days. Discontinuation of cadmium exposure for 28 days failed to restore normal adrenal weights in the 1.0 mg/kg animals, but CA levels returned to control values, as did TH activity. These results suggest that cadmium exerts significant, although apparently reversible effects, on adrenal medullary CA synthesis at i.p. dose levels as low as 0.25 mg/kg.

Adrenal cortical functions, as well as adrenal medullary secretions, appear to be affected by cadmium, according to a study by Der et al. (1977a), which compared the effects of cadmium and lead on thyroid and adrenal functions. Adult male rats weighting 300 ± 5 g received daily intramuscular (i.m.) injections of 50 or 250 μg of cadmium chloride, while other rats received either 50 or 250 μg of lead or simultaneous injections of 25 μg each of lead acetate and cadmium chloride. Significant deficits in weight gain and increased adrenal weights were observed during 70 days

of cadmium exposure at the 250 μg dose. Also, adrenal histology evaluations revealed increased nuclear diameters in cells of the zona glomerulosa and fasciculata of both the 50- and 250-μg cadmium-dose groups; and plasma corticosterone levels were found to be significantly elevated in the 50- and 250-μg cadmium groups and the combined 25-μg lead-cadmium group. These results provide evidence for adrenal cortical hypertrophy after chronic cadmium treatment, resulting in increased adrenal corticosteroid secretion. It remains to be seen, however, as to whether such effects occur after exposure to cadmium via oral ingestion or inhalation.

2.8.4 Thyroid Effects

The demonstration of high thyroid cadmium levels in human autopsy material (Friberg, 1957), as for the pancreas, raises the possibility of the thyroid being a target organ for the metal. Relatively sparse information, however, exists concerning cadmium effects on the thyroid. In the Der et al. (1977a) study mentioned earlier, evidence was found for significant decreases being induced in plasma T_4 levels in rats by the 250 μg cadmium chloride treatment and in plasma T_3 levels by the 50 μg and 250μg cadmium doses as well as by the combined 25 μg lead and cadmium treatment. No evident changes in thyroid histology accompanied the decreases in thyroid hormone secretion seen with any of the treatments. Nevertheless, Der et al. (1977a) hypothesized that the hypothyroid state induced by cadmium might be responsible for a decreased rate of body weight gain observed for the 250 μg cadmium dose group and might also contribute to increased susceptibility to various disease resulting from cadmium-induced immune suppression effects.

2.8.5 Pituitary Effects

An important point to consider in the interpretation of the above endocrine effect studies is the difficulty that exists in disentangling possible direct effects of cadmium on the endocrine organs discussed from effects that may be exerted via cadmium actions on the pituitary and vice versa. At least a few examples have been cited in regard to changes in the pituitary itself after cadmium exposure. One such effect is the decrease in pituitary weight reported by Der et al. (1977a) after exposure of female rats to 250 μg cadmium chloride for 54 days.

Other pituitary effects seen after cadmium include hyperplasia of gonadotropic cells and increased numbers of prolactin secreting cells in the anterior pituitary of male rats as revealed by immunofluorescence methods (Girod and Dubois, 1974, 1976). Consistent with this observation is the reported increase in plasma leuteinizing hormone (LH) level (Chandler et al., 1976) seen in cadmium-exposed rats for which ultrastructural evidence was obtained for changes in the entire interstitial-tubular complex of the male reproductive tract. Whether the observed pituitary cytology changes and LH increases represent a direct effect of cadmium on the pituitary or occur secondarily to damage to the testes by the metal presently is not clear. The possibility remains that at least some endocrine-related effects associated with cadmium exposure may be exerted via cadmium effects on the pituitary directly, and this possibility is reinforced by the Berlin and Ullberg (1963) finding of some accumulations of cadmium in that gland.

2.9 EFFECTS OF CADMIUM ON BONE AND MINERAL METABOLISM

The effects of cadmium on bone arises from chronic exposure, and this derangement appears to be secondary to renal malfunction through disturbance

in calcium and phosphorus metabolism. The literature detailing the effects of cadmium on calcium metabolism and bone structure in experimental animals suggests that this may indeed be the case.

2.9.1 Animal Studies

In the studies of Kawai and coworkers (1974), in which rats were chronically dosed with cadmium (10 to 200 μg Cd/ml in drinking water, up to 8 1/2 mo), histological findings in the bone appeared in the 50 ppm Cd group, and higher exposure levels were associated with decalcification and cortical atrophy of the femur. Calcium content also was reduced in the highest level (200 (μg/ml) exposure group.

The data of Itokawa et al. (1974) demonstrated effects of cadmium on bone in rats using an exposure level of 50 ppm in water and either calcium-adequate or calcium-deficient diets. In both of the cadmium-treated groups, urinary calcium and phosphorus levels were significantly reduced, with thinning of the cortical osseous tissue seen in bones of cadmium-exposed animals which were fed a calcium-deficient diet. Furthermore, fat deposition occurred in the femoral spongiosa in both cadmium groups, while the cadmium-exposed animals on the low-calcium diet manifested osteoid borders on trabeculae and an increased number of osteocytes. These authors pointed out the similarity of this osteopathology with the osteomalacia seen in man. This osteopathology may be secondary to early renal glomerular damage occurring before the onset of tubular dysfunction.

Abe et al. (1972) gave rats cadmium in diet corresponding to a daily ingestion of 1.5 mg and observed after 4 wk that this dosing regimen, along with diets low in protein and calcium, led to abnormal curvature of the spine.

Reference was made in the section on renal effects (2.5) to the inhibitory action of cadmium on the conversion of 25-hydroxy-Vitamin-D_3 to the physiologically active essential metabolite, 1,25-hydroxy-Vitamin-D_3. Sugawara and Sugawara (1974) observed decreased calcium absorption in rats receiving 50 ppm cadmium in drinking water. Also, in a recent report, Kawai (1976) noted decalcification and cortical atrophy in bone tissue with chronic dietary exposure to cadmium.

2.9.2 Human Aspects

In man, osteomalacia and severe osteoporosis are known effects of chronic cadmium exposure, in both occupational settings and in populations sustaining pronounced cadmium exposure (Nordberg, 1976; Friberg et al., 1974).

As noted elsewhere, Itai-Itai disease is a patho-physiological triad of renal tubular dysfunction, osteoporosis, and osteomalacia. There appears to be no question that there is a nutritional component to the manifestation of the disease: calcium and Vitamin-D deficiency in postmenopausal women with a history of multiple childbirth and past probable deficiency in these two factors. Osteopathic symptomatology (Friberg et al. 1974) of the disorder includes: Milkman's pseudo-fractures and fractures, thinned bone cortex, decalcification, deformation, fishbone vertebrae, and coxa vara. Biochemical changes include decreased serum P_i and a decreased urinary P/Ca ratio.

2.10 HEPATIC EFFECTS OF CADMIUM

Although hepatic tissue is one of the sites where cadmium accumulates and induces functional alteration, the literature is not so extensive as that which exists for renal, pulmonary, and cardiovascular effects. Liver

is the major biosynthetic organ for metallothionein in a number of experimental animal species and man, so any consideration of the extent of hepatic functional derangements as a function of the amount of cadmium present in liver must take this factor into account.

2.10.1 Animal Studies

It was noted earlier that cadmium, at high doses, has an effect on the drug-detoxifying actions of enzyme complexes, as measured by several techniques, including sleeping-time changes and enzyme inhibition.

Further animal studies have been carried out on the hepatic effects of cadmium under varying experimental conditions. For example, Andreuzzi and Odescalchi (1958) found that rabbit serum glutamic-oxaloacetic-transaminase was elevated following intravenous administration of cadmium (1.25 to 3.0 mg/kg, 24 to 72 hr), with a ten-fold or greater increase after 24 hr using the largest dosage, which killed 60 percent of the animals within 24 hr. These workers concluded that a dose approaching the LD_{50} was required to produce severe liver lesions, while lower exposure effects were reversible.

Neige et al. (1974) showed that rats given 4 subcutaneous injections per week of cadmium sulfate (3 mg Cd/wk) displayed, after 60 days, cytoplasmic necrosis of hepatocytes, festooning of nuclear membranes, and round intra-nuclear inclusions.

Colucci et al. (1975) induced pathological changes in rat hepatic tissue by the i.p. injection of cadmium (0.5 to 4.0 mg/kg, t to 6 days). Animals in the 0.5 and 1.0 mg Cd/kg groups showed no microscopic hepatic abnormalities. Those in the higher dose groups revealed degenerating hepatocytes. These workers found that, when liver cadmium levels were below 30 μg Cd/g wet weight, the metal was sequestered as metallothionein,

and no apparent toxicity was evident. Levels of 40 μg Cd/g were associated with hepatic cellular degeneration as well as other systemic pathology.

Faeder et al. (1977) investigated biochemical ultrastructural changes in hepatic tissue of rats exposed to cadmium at levels known to induce hepatic changes but administered so as to minimize clinical signs of morbidity (subcutaneous injection, 0.25 to 0.75 mg Cd/kg, 3 times/wk for 8 wk). After 6 wk, animals given 0.5 mg/kg showed dilation and loss of ribosomes from the endoplasmic reticulum, with the additional feature of swollen mitochondria observed at the 0.75 mg/kg dose level. Biochemically, plasma aspartate aminotransferase (AAT), α-glutamyl transpeptidase, and erythrocyte carbonic anhydrase activities were elevated by the sixth week of exposure.

Sequential changes in hepatic polyamine, DNA, and cyclic AMP metabolism were reported by Kacew et al. (1977) in rats subacutely exposed to cadmium (1 mg/kg, twice a day for 3, 5 and 7 days). Hepatic levels of spermidine and spermine were significantly lowered while hepatic DNA synthesis was increased. Stimulation of the hepatic adenylate cyclase-cyclic AMP system was noted to occur as early as 1 day.

It should be noted that morphological changes in the liver occur before changes in hepatic marker enzymes activities.

2.10.2 Human Aspects

While an acute effect of cadmium on liver function in occupationally exposed men has been seen, liver disturbances are not a common finding in the human toxicity of cadmium; and gross changes are quite rare (Friberg et al., 1974).

2.11 NEUROLOGICAL EFFECTS OF CADMIUM

Perhaps not surprising in view of the relatively low uptake of cadmium into brain and other neural tissue, potential neurological effects of cadmium have been accorded much less attention in the research literature than many other types of cadmium effects. Only a few studies of humans occupationally exposed to cadmium have provided any evidence for cadmium-induced neurological damage, and that has been largely confined to apparent deficits in sensory functions. Also, comparatively little convincing evidence for neural effects has been demonstrated by the limited number of animals studies that have been conducted.

In regard to human studies, Friberg (1950) reported that 37 percent of 43 cadmium-exposed workers studied had olfactory impairments. Those workers, however, were also exposed to nickel dust. Adams and Crabtree (1961), too, found evidence for hyposmia and anosmia when they compared a group of 106 battery workers exposed to cadmium oxide and nickel dust to 84 age-matched, non-exposed control subjects. Significantly more battery workers reported themselves to be anosmic than control subjects (15 vs 0 percent, respectively), and they did less well than controls on a phenol-smelling test. Anosmia correlated well with proteinuria, with 17 battery workers exhibiting proteinuria also being anosmic. Signs of local nasal irritation, ulceration, and dry crusting suggested likely direct damage to the olfactory mucosae. Olfactory impairment in the same worker population was also found by Potts (1965) in 53 to 65 percent of the battery-factory workers exposed 10 to 29 years to cadmium oxide dust and in 91 percent exposed for over 30 years; again, the workers were likely exposed to nickel as well as

cadmium. Tsuji et al. (1972), on the other hand, reported impaired olfaction in workers exposed to cadmium at a zinc refinery, where no concomitant nickel exposures were encountered. While these results suggest that cadmium may cause direct damage to nasal olfactory mucosae, it should be noted that such effects apparently only occur at extremely high inhalation exposure levels that were previously of concern in industrial situations; and little evidence for such effects at lower exposure levels has yet been provided by animal or human studies.

About the only other report of signs of possible cadmium-induced neural damage in humans is that of Vorob'yeva (1957) on changes in the "chronaxies" of cutaneous sensory and optic nerves of cadmium-exposed workers, but, again, little confirmation of any peripheral nerve damage has come from other human or animal studies.

What little evidence from animal studies that exists for cadmium effects on neural tissue comes mainly from in vitro work. This includes reports that cadmium chloride exerts toxic effects on gasserian and spinal sensory ganglia (Gabbiani et al., 1967a; Schlaepfer, 1971), cerebellar tissue (Kasuya et al., 1974), and other central nervous system (CNS) tissue (Gabbiani et al., 1967b). Pathological changes observed by Kasuya et al. (1974) included inhibition by cadmium stearate of normal outgrowth of cerebellar cells cultured from brains of newborn rats. Still other effects of cadmium on neural functions have been demonstrated in vitro. Edstrom and Mattson (1976), for example, studied the effects of sulfhydryl blocking agents on the in vitro rapid axonal transport of ^{3}H-leucine-labelled proteins in the frog sciatic nerve. Rapid transport of the proteins was inhibited in the presence of low concentrations of divalent heavy metals including cadmium.

Research in other studies has focused on possible molecular mechanisms by which cadmium might affect neurotransmission, with some consistent results emerging from such studies. In one study, Kamino et al. (1975) utilized synaptosomes isolated from rat brain cortex to investigate the effects of cations on cynaptosomal CA^{++}-binding. Cadmium, as well as other cations tested, significantly inhibited synaptosomal Ca^{++}-binding, suggesting possible disruptive effects on presynaptic transmitter release or uptake mechanisms.

Consistent with the above interpretation, several studies have demonstrated cadmium effects on neurotransmission, including effects on release of particular transmitters. In that regard, Chen (1975) studied the effects of divalent cations and catecholamines on the "late response" of the superior cervical ganglion of dogs and found that catecholamines suppress that response, while certain divalent ions such as cadmium potentiate and prolong it. Chen (1975) concluded that cadmium chloride may inhibit sympathetic ganglionic transmission by presynaptic suppression of acetylcholine release. Similar conclusions were reached by Toda (1976) and Forshaw (1977), who presented evidence for inhibitory effects of cadmium on neuromuscular transmission in isolated frog striate muscle and isolated rat diaphragm, respectively. Toda (1976) concluded from his overall data that cadmium interferes with the release of acetylcholine from motor nerve terminals by reducing the transmembranous influx of calcium, and Forshaw (1977) concluded that cadmium reduced the quantal release of transmitter in the isolated phrenic diaphragm by inhibition of calcium function at presynaptic nerve terminals. Cooper and Steinberg (1977) reported results

they interpreted as indicating that cadmium blocked adrenergic neuromuscular transmission in the rabbit primarily through an effect on presynaptic nerve terminals.

Ribas-Ozonas et al. (1974) reported decreases in regional brain serotonin (5-hydroxytryptamine, 5-HT) levels after intraventricular injection of a 33 μg dose of cadmium chloride 1 to 3 days before the injected rats were sacrificed. Subsequently, Hrdina et al. (1976) studied the effects of chronic (45 days) i.p. injections of doses of cadmium chloride (0.25 and 1.0 mg/kg/day) on the regional levels of brain neurotransmitters and associated enzymes. Both doses of cadmium produced significant decreases in cortical acetylcholine and brainstem 5-HT and a transient increase in striatal dopamine. Cadmium-induced decreases in brain 5-HT levels persisted even after withdrawal of cadmium treatment for 28 days before sacrifice. Hrdina et al. (1976) suggested that alterations in brain amine levels seen after cadmium treatment may represent early signs of adverse effects on CNS function, but caution must be exercised before accepting such a conclusion. For example, the relevance for present purposes of injections of relatively high amounts of cadmium directly in the cerebroventricular system is highly questionable in view of data showing that only very low amounts of cadmium accumulate in brain tissue after systemic administration. Also, in view of cadmium's poor entry into brain, the changes in brain neurotransmitters seen by Hrdina et al. (1976) after chronic i.p. injections might be more appropriately attributed to secondary effects (possibly differential overall stress associated with cadmium exposure) rather than to direct effects of the metal on brain tissue.

Very few studies have been reported that attempt to relate cadmium exposures to neurotoxic effects manifested in terms of learning or other behavioral deficits. For example, in the Krasovskii et al. (1976) study reviewed earlier in the section on reproduction and development, it was claimed that "changes" in the conditioned reflex activity of experimental animals" were seen with oral exposures to 0.005 and 0.0005 mg/kg doses of cadmium chloride. In another study (Pihl and Parkes, 1977) hair samples from 31 learning disabled and 22 normal children were analyzed for content of 14 elements, including cadmium and lead; and significantly higher levels of cadmium and several other metals were reported to be found in the hair of the learning-disabled group. Given the widely recognized difficulties with hair cadmium determinations, however, these results require further confirmation.

2.12 GASTROINTESTINAL EFFECTS OF CADMIUM

Acute gastrointestinal effects of cadmium are quite uncommon in man, chiefly because the occurrence of acute cadmium poisoning by ingestion in man is rare. Chronic gastrointestinal effects of cadmium have only been seen in victims of Itai-Itai disease (Friberg et al., 1974).

In animals, studies do exist regarding the gastroenterological toxicity of cadmium. For example, shortening and thickening of mucosal villi in the duodenum of Japanese quail are seen when cadmium exposure occurs through the diet (Richardson et al., 1974) at comparatively high levels. In addition, marked hyperplasia of duodenal goblet cells occurs after 4 wk.

In a second study using Japanese quail (Richardson and Fox, 1974) cadmium fed to the birds at a level of 75 mg/kg diet from hatching to 1 mo of age led to gross, microscopic, and ultrastructural lesions in the proximal

small intestines. For example, the small intestines were dilated and thin-walled, hypertrophy and hyperplasia of goblet cells occurred, microvilli of both absorptive and goblet cells were markedly shortened, and absorptive cells were atrophic and mitochondria were dense and small. Interestingly, these lesions resemble the pathological picture seen in human malabsorption syndromes, tropical and nontropical sprue, and celiac disease.

Valberg et al. (1977) assessed the relative sensitivity of mouse intestinal mucosa to cadmium-thionein and inorganic salt (cadmium chloride). Using open-ended duodenal perfusion, equivalent amounts of cadmium in either form entered the mucosa. Free cadmium ion occasioned minor derangement in the form of villi broadening and mitochondrial swelling while the protein-bound cadmium resulted in considerable damage to absorptive cells. These effects are contrasted to the observation that little bound cadmium entered the body compared with the inorganic form.

This provides further evidence (see: Renal Effects and Hepatic Effects sections) that cadmium-thionein plays a two-fold role in cadmium toxicity, i.e., on-site protection is afforded in some organs such as liver and intestinal tract while release of the cadmium-thionein from these same organs to extracellular fluid presents cadmium in a form that is functionally more toxic than the inorganic form on an equivalent metal-content basis.

2.13 HEMATOLOGICAL EFFECTS OF CADMIUM

Unlike lead, where a number of hematological effects are seen over a range of that toxic element's exposure levels, comparatively less is known of the effects of cadmium on the hematopoietic system of man and experimental animals. Hematological effects appearing in the earlier literature

have been reviewed (Friberg et al., 1974); Fulkerson and Goeller, 1973; Nordberg, 1974).

Cadmium-induced anemia has been observed in man from industrial exposure and in animals. The anemia is moderate, is claimed to have hemolytic and iron-deficiency components (Nordberg, 1976), and in animals appears rather early in cadmium exposure.

Prigg et al. (1977) studied the effects of dietary and inhalation cadmium on hemoglobin and hematocrit in rats as a way of assessing whether the anemia induced is related to impaired iron absorption or erythrocyte destruction. It appears that erythrocyte destruction is not a major factor in rats, since the cadmium aerosol treatment failed to elicit any anemia. In the dietary-cadmium groups (25, 50, and 100 ppm Cd in drinking water), there was a significant reduction in hematocrit and hemoglobin values, in accord with the observations of others (Fox et al., 1971; Maji and Yoshida, 1974; Freeland and Cousins, 1973).

It has also been observed that dietary iron supplement (Fox et al., 1971; Maji and Yoshida, 1974) or injected iron (Pond and Walker, 1972) restores the levels of hemoglobin and the hematocrit to normal.

The effect of cadmium on erythrocyte δ-aminolevulinic acid dehydratase (δ-ALA-D) has been studied in several animal species. Seth et al. (1976) saw no effect on δ-ALA-D) activity when mice were given cadmium by i.p. injection (2 mg Cd/kg, with and without co-injection of lead). Lynch et al. (1976), however, induced significant inhibition of δ-ALA-D activity when calves were given cadmium alone or with lead (15 mg Cd/kg body weight) contained in gelatin capsules.

Roels et al. (1975) could not find any relationship between cadmium and erythrocyte δ-ALA-D activity in a group of 84 workers in a cadmium works. In this case, erythrocyte metallothionein probably provided a protective function.

2.14 IMMUNOSUPPRESSIVE EFFECTS OF CADMIUM

Heightened susceptibility to the toxic effects of infectious agents has been demonstrated with cadmium exposure via several different routes, including systemic injections and oral administration of the metal. In a study by Cook et al. (1975b), the relative potency of lead and cadmium were compared in regard to the potentiation of an endotoxin. Neither lead acetate injected into rats intravenously at a dose of 2.25 μmol/100 g nor minute quantities of S. enteritidis endotoxin alone were lethal, whereas a single intravenous dose of cadmium acetate at 2.25 μmol/100 g produced a mortality of 5 percent. Simultaneous injection of cadmium acetate with the endotoxin potentiated the otherwise mild effects of the toxin much more than did lead, with 94 percent mortality being induced by cadmium and only 31 percent by lead. Also, when different doses of endotoxin were injected with the same dose of cadmium or alone, it was found that a dose of endotoxin as low as 0.12 μg/100 g produced 40 percent mortality when injected along with cadmium but a 12,500-times higher dose of the toxin was necessary to produce equivalent mortality when injected alone. By injecting the endotoxin before, with, or after cadmium, it was found that the greatest synergism occurred when the endotoxin was injected together with cadmium (94 percent mortality) rather than either 4 to 8 hr before (0 percent mortality) or after (10 to 50 percent mortality). Cook et al. (1975b) discuss possible mechanisms by which cadmium might exert its endotoxin-

potentiating effects and report ultrastructural evidence implicating liver damage as one important factor.

In another series of studies, Koller and coworkers have also recently reported some evidence for immunosuppressive effects of cadmium administered via oral exposure. Koller (1973) reported that rabbits exposed 70 days to mercuric chloride, cadmium chloride, or lead acetate in drinking water (at doses of 10, 300, or 2,500 ppm, respectively) had significantly lower neutralizing antibody titers after inoculation with a pseudorabies virus.

Evidence for cadmium-induced increased susceptibility to disease in mice was also serendipitously observed in a subsequent study to Exon et al. (1975). Cadmium-stressed mice being used in the study for other purposes began dying from an intestinal infection later identified as due to Hexamita muris. Mice that had been exposed for 4 to 5 wk to 3 or 300 ppm of cadmium as cadmium chloride in the drinking water experienced 7 percent and 26 percent mortality, respectively. No deaths occurred, however, in non-exposed control animals. Interestingly, no "typical" cadmium lesions were found in any organs of cadmium-exposed animals, suggesting that immunosuppressive effects may be induced at substantially lower exposure levels than those required to induce other, classically defined cadmium effects.

More direct evidence for immunosuppressive effects in mice was reported by Koller et al. (1975). Mice exposed orally to "subclinical" doses, i.e., 3 or 300 ppm, of cadmium chloride in drinking water for 70 days experienced marked decreases in antibody-forming spleen cells, especially IgG cells, which persisted in the 300 ppm dose rats for at least six weeks after cessation of cadmium exposure. Such results suggest that immunosuppressive effects of cadmium, including that absorbed via chronic oral ingestion, may persist for quite some time after the cessation of high-level exposures.

Speculation concerning the mechanisms by which cadmium exerts its immunosuppressive effects include possible interactions with the infectious agent itself or damaging effects on various immune system cellular components. In regard to the latter possibility, Koller and Roan (1977) assessed whether mouse peritoneal macrophages were damaged by cadmium. Cadmium chloride was given orally for 10 wk at doses of 3, 30, or 300 ppm in drinking water, and the functional integrity of peritoneal macrophages was assessed. Since phagocytotic activity and acid phosphatase levels were increased in the macrophages, it was concluded that the metal activates macrophages. Based on this, it appears unlikely that immunosuppressive effects of cadmium are exerted through damage to macrophages. On the other hand, Waters et al. (1975) reported evidence for cytotoxic effects of cadmium on rabbit alveolar macrophages assessed in an in vitro model system.

In summary, it appears that cadmium does exert immunosuppressive effects both in vitro and in vivo. Furthermore, the metal appears to be many times more potent than other immunosuppressive heavy metals in potentiating certain toxic effects of various infectious agents. Lastly, the immunosuppressive action of cadmium seems, at times, to persist beyond cessation of oral exposure. Effects such as these, however, still remain to be demonstrated with human cadmium exposure.

2.15 MUTAGENIC AND CARCINOGENIC EFFECTS OF CADMIUM

Considerable concern has been generated by reports of association of cadmium exposure with mutagenesis or carcinogenesis in animals or humans. Several relevant reviews have recently appeared which deal with mutagenic effects of cadmium, the experimental induction of tumors in animals, or human cancer epidemiology studies (Flick et al., 1971; IARC, 1976; NIOSH,

1976; Sunderman, 1977; Carcinogen Assessment Group, 1978). As reviewed in these reports, much information has emerged in regard to the conditions under which mutagenic or tumorigenic effects can be generated experimentally in animals, whereas far less data are currently available regarding the carcinogenic potential of cadmium in humans. Still, as noted below, similar conclusions have been drawn as a result of most of the relevant reviews; that is, the assessments have typically led to the conclusion that presumptive evidence exists for cadmium-induced mutagenic and carcinogenic effects.

2.15.1 Mutagenic Effects of Cadmium

Numerous studies have focused on assessment of the mutagenic properties of cadmium, and considerable evidence has been obtained for cadmium-induced mutagenicity in various test systems. The results of many of the more salient studies are summarized in Table 2-7.

As indicated in Table 2-7, evidence for cadmium-induced mutagenic effects has been obtained *in vitro* with several different test systems. Such evidence includes, for example, the demonstration of: (1) statistically significant increases in mispaired nucleotides when cadmium chloride was added to an *in vitro* DNA synthesis system (Sirover and Loeb, 1976); (2) abnormal mitotic and meiotic recombinations in the yeast, *Sacharomyces cerevisiae*, upon exposure to cadmium chloride (Takahashi, 1972); (3) production by cadmium chloride, but not cadmium nitrate, of mutant recombinants in strains of *Bacillus subtilis* (Nishioka, 1975) (4) unscheduled DNA synthesis in Chinese hamster embryo cells following exposure to cadmium chloride and cadmium acetate (Costa *et al.*, 1976); and (5) the induction by cadmium sulfide of chromosomal aberrations in cultured human leukocytes

Table 2-7. SUMMARY OF MUTAGENICITY TEST RESULTS

Test system	Genetic effect	Reported mutagenicity	References
	Systems in vitro		
Human cells	Chromosomal damage	+	Shiraishi *et al.* (1972)
Chinese hamster cells	Point mutation	+	Costa *et al.* (1976)
S. cerevisiae	Point mutation	+	Takahoshi (1972)
B. subtilis-recombinant assay	Gene mutation	+	Nishioka (1975)
Polynucleotides	Base mispairing	+	Sirover and Loeb (1976)
	Systems in vivo		
Human leukocytes	Chromosomal damage	+	Shirashi and Yoshida (1976)
Human leukocytes	Chromosomal damage	-	Bui *et al.* (1975)
Human leukocytes	Chromosomal damage	+	Deknudt and Leonard (1975)
Human leukocytes	Chromosomal damage	+	Bauchinger *et al.* (1976)
Mouse oocytes	Cytogenetic damage	+	Shimada *et al.* (1976)
Mouse breeding	Dominant lethal mutations	-	Epstein *et al.* (1972)
Mouse breeding	Dominant lethal mutations	-	Gilliavod and Leonard (1975)
Mouse breeding	Dominant lethal mutations	-	Suter (1975)
Mammals	Chromosomal abnormalities	-	Shimada *et al.* (1976)
D. melanogaster	Sex-linked recessive lethal	-	Sorsa and Pfeifer (1973)

(Shiraishi et al., 1972). Specific types of human chromosomal aberrations seen in the latter in vitro study, it should be noted, were similar to those reported for human leukocytes obtained from Itai-Itai disease patients (Shiraishi and Yoshida, 1972). Thus, in summary, mutagenic effects on genetic material or cells from a variety of species, ranging from yeast and bacteria to hamsters and humans, have been demonstrated to occur in vitro with exposure to several different cadmium compounds. The latter effects appear to be analogous to in vivo effects observed in certain human, high-level cadmium exposure cases. When considering the in vitro cadmium mutagenicity data, it must be kept in mind that, in the human or other mammalian organisms, cadmium is mainly bound to metallothionein and other proteins, and there is little evidence for ionic cadmium being present in substantial amounts.

Also as indicated in Table 2-7, several studies have yielded evidence of in vivo mutagenic effects of cadmium at high exposure levels. This includes the demonstration of (1) numerical chromosomal anomalies in mouse oocytes and blocked development of metaphase I chromosomes following injection of an acute dose of 3 or 6 mg/kg of cadmium chloride (Shimada et al., 1976); and (2) chromosomal damage in human leukocytes obtained from Itai-Itai patients (Shiraishi and Yoshida, 1972) or workers exposed to cadmium and lead (Deknudt and Leonard, 1975; Bauchinger et al., 1976).

In regard to in vivo studies finding no mutagenic effects, the one test yielding consistently negative results is that for dominant lethal mutations. In one study (Epstein et al., 1972), for example, cadmium chloride was among 174 compounds evaluated for ability to induce dominant lethal mutations in mice, but no significant evidence was obtained for the

cadmium compound having such mutagenic activity at i.p. doses ranging from 1.35 to 1.70 mg/kg. Nor was any evidence for such cadmium-induced mutagenicity in mice obtained in a similar study by Gilliavod and Leonard (1975), using i.p. injections of 0.5, 1.75, or 3.0 mg/kg of cadmium chloride, or in a study by Suter (1975), in which cadmium chloride (2 mg/kg, i.p.) had no detectable dominant-lethal effects in female mice.

The results of some of the above negative studies and certain others listed in Table 2-7 have been criticized (Troast, 1978) as not being sufficiently sensitive to mutagenicity for an accurate evaluation (Gilliavod and Leonard, 1975; Sorsa and Pfeifer, 1973) or for lacking sufficient sample numbers (Bui et al., 1975). Also, the results of Deknudt and Leonard (1975) and Bauchinger et al. (1976) may in part be due to lead as well as cadmium, since the human subjects in each of the two studies experienced exposure to both metals. Overall, the studies reviewed here and in Table 2-8 mainly provide evidence for cadmium-induced mutagenicity at high concentrations and especially with in vitro test systems. Little or no data exists for mutagenic effects occurring with oral or inhalation exposure of humans. The significance of in vitro mutagenic effects beyond their immediate implications for disruption of genetic processes in artificial testing systems therefore remains to be seen. In fact, while mutagenic properties of some compounds may correlate with their carcinogenic potential, this does not appear to hold very well in the case of cadmium or other heavy metals. Therefore, in vitro mutagenetic effects of cadmium do not necessarily imply that the element is also carcinogenic.

2.15.2 Tumorigenic Cadmium Effects in Animals

Numerous studies have demonstrated the induction of tumors at sites of subcutaneous or intramuscular injections of cadmium. In that regard,

Sunderman (1977) reviewed data showing that parenteral injections of cadmium powder or cadmium sulfide, oxide, sulfate, or chloride in rodents induced sarcomas at the site of injection, as also reported in a number of studies summarized in Table 2-8 (which is modified from one presented by Sunderman, 1977). In addition to injection-site sarcomas being produced, subcutaneous injection of cadmium chloride, even at a distance from the testes, often induced testicular necrosis followed by Leydig cell regeneration and hyperplasia and ultimately Leydig cell tumors of "Leydigiomas" (Haddow et al., 1964; Roe et al., 1964; Guthrie, 1964; Gunn et al., 1963, 1964, 1965, 1967; Nazari et al., 1967; Favino et al., 1968; Knorre, 1970, 1971; Lucis et al., 1972, Reddy et al., 1973). The Leydig cell tumors thusly produced have often been found to be functionally active in the sense of secreting large amounts of sex steroids (Gunn et al., 1965; Favino et al., 1968; Lucis et al., 1972; Reddy et al., 1973). Typically, high-level, systemic-injection doses have been employed to produce injection-site sarcomas or distal-site tumors, with effective doses of cadmium often exceeding 1.0 mg/kg of body weight.

Leydig cell tumors observed after systemic injections of cadmium in the above manner, however, have not yet been found to increase in incidence when cadmium is administered orally at lower dose levels (Schroeder et al., 1965; Kanisawa and Schroeder, 1969; Levy and Clack, 1975; Levy et al., 1975). Schroeder et al. (1965) and Kanisawa and Schroeder (1969) exposed rats to cadmium acetate in their drinking water (at 5 ppm) from weaning until death up to four years later and found no significant increase in tumors for cadmium-exposed animals in comparison to the incidence for control animals.

Table 2-8. STUDIES ON CADMIUM TUMORIGENESIS IN EXPERIMENTAL ANIMALS[a]

Author(s)	Animals	Compound and route(s)	Lowest effective dose	Injection site	Tumor site	Type of tumors
Heath *et al.*, 1962	Rats	Cd powder in fowl serum (im[b])	One dose of 0.014 gm	Thigh muscle	Thigh muscle and lymph nodes	Sarcomas
Heath and Daniel, 1964	Rats	Cd powder in fowl serum (im)[b]	One dose of 0.014 gm	Thigh muscle	Thigh muscle and lymph metastases	Sarcomas
Kazantzis, 1963	Rats	CdS (sc)[b]	Two doses of 25 mg ea.	Dorsal sc[b] tissue	Injection site	Sarcomas
Kazantzis and Hanbury, 1966	Rats	CdS (sc)[b]	One dose of 25 mg	Dorsal sc[b] tissue	Injection site plus lung, spleen, stomach, and pancreas	Sarcomas
		CdO (sc)[b]	One dose of 25 mg	Dorsal sc[b] tissue	Injection site	Sarcomas
Haddow *et al.*, 1964	Rats	$CdSO_4$ in rat ferritin (sc)[b]	Ten doses of 20 mg ea.	Right flank	Right flank	Sarcomas
		$CdSO_4$ (sc)[b]	Ten doses of 0.5 mg ea.	Right flank	Right flank and Leydig cell	Sarcomas; Leydigomas
Roe *et al.*, 1964	Rats	$CdSO_4$ (sc)[b]	Ten doses of 0.5 mg ea.	Flank	Flank and testis	Sarcomas; Leydigomas
Guthrie, 1964	Chickens	$CdCl_2$ (intercostal injection)	One dose of 2% solution; amount not given	Intratesticular via intercostal injection	Testis	Teratoma

Table 2-8 (continued). STUDIES ON CADMIUM TUMORIGENESIS IN EXPERIMENTAL ANIMALS[a]

Author(s)	Animals	Compound and route(s)	Lowest effective dose	Injection site	Tumor site	Type of tumors
Gunn *et al.*, 1963	Rats; Mice	$CdCl_2$ (sc)[b]	One dose of 0.03 mmole/kg (3.372 mg/kg)	Subcutaneous (--)[c]	Testis (interstitial cell)	Interstitial cell tumors
Gunn *et al.*, 1964	Rats	$CdCl_2$ (intracapsular)	One 0.4 ml dose of 0.03 M (equivalent to 1.35 mg (d ion)	--[c]	Injection site; testis (interstitial cells)	Sarcomas and Leydigomas
Gunn *et al.*, 1965	Rats	$CdCl_2$ (sc)[b]	One dose of 0.03 mmole/kg (3.372 mg/kg)	Subcutaneous (--)[c]	Testis	Interstitial cell tumors
Gunn *et al.*, 1967	Rats	$CdCl_2$ solution	One dose of 0.17 Cd ion	Ectoderm; intracutaneous (chest); endoderm; salivary gland; liver; ventral prostate; epithelial mesoderm; kidney; mesenchymal mesoderm, sc[b] (intracapsular); im[b] (thigh); subperiosteal (femur)	Subcutaneous	Sarcomas
Schroeder *et al.*, 1965	Rats; mice	Cd-acetate (drinking water)	5 ppm Cd in drinking water	Diet	Similar to controls	Similar to controls

Table 2-8 (continued). STUDIES ON CADMIUM TUMORIGENESIS IN EXPERIMENTAL ANIMALS[a]

Author(s)	Animals	Compound and route(s)	Lowest effective dose	Injection site	Tumor site	Type of tumors
Kanisawa and Schroeder, 1969						
Nazari *et al.*, 1967 Favino *et al.*, 1968	Rats	$CdCl_2$ (sc)[b]	--[c]	--[c]	--[c] and testis	Sarcomas and Leydigomas
Knorre, 1970	Rats	$CdCl_2$ (sc)[b]	Equivalent to ~5.5 mg/kg	Left hip	Skin and muscle at injection site	Sarcomas
Lucis *et al.*, 1972	Rats	$CdCl_2$ (sc)[b] intrahepatic	0.02 mM/kg (2.248 mg/kg)	--[c]; liver	Injection site; testis	Sarcomas and Leydigomas
Reddy *et al.*, 1973	Rats	$CdCl_2$ (sc)[b]	0.03 mmole/kg (3.372 mg/kg)	--[c]	Testis	Leydigomas
Levy *et al.*, 1973	Rats	$CdSO_4$ (sc)[b]	Weekly injections of 0.05 mg ea. for 2 yr	Flank	Flank	Sarcoma and other neoplasms
Levy *et al.*, 1975	Mice	$CdSO_4$ (stomach tube)	Weekly injections of up to 4 mg/kg for 18 mo	Diet via tube	--[c]	No tumorigenic effect

[a]Adapted from Sunderman, 1977.
[b]Intramuscular: im; subcutaneous: sc.
[c]Information unavailable: --

Also, in the studies by Levy and coworkers, cadmium sulfate was administered to rats by direct gastric intubation 3 times per wk for 2 yr (at doses of 0, 87, 180, or 350 μg Cd/kg) and to mice by the same procedure carried out once per wk for 18 mo (at doses of 0, 0.44, 0.88, or 1.75 mg Cd/kg). No significant increases in the incidence of Leydig cell tumors were found for the cadmium-treated animals, nor were any prostate neoplasms or pre-neoplastic changes in the prostate seen in the cadmium-exposed groups.

The Schroeder and the Levy studies cited above that found no tumorigenic effects after oral cadmium administration have been found to be inconclusive, as evaluated by other working groups (IARC, 1976; Carcinogen Assessment Group, 1977) and the present authors. The doses employed in the various Schroeder and Levy studies resulted in kidney concentrations of cadmium below those typically seen in adult humans. Lastly, certain problems associated with only some animals being sampled for possible tumor pathology and some results being stated only in qualitative terms rather than quantitatively make adequate interpretation of aspects of the studies very difficult.

Based on the collection of other, positive results discussed here, it appears that tumorigenic effects can be induced by cadmium following its systemic injection at very high concentration levels, with sarcomas commonly occurring at the injection site or Leydig cell tumors developing at a distance from the injection site. This latter effect in particular has been taken (IARC, 1976; NIOSH, 1976; Carcinogen Assessment Group, 1978) as being somewhat suggestive of carcinogenic potential existing for cadmium;

but far stronger evidence for carcinogenicity is needed before any convincing case can be made for its being carcinogenic at environmentally relevant exposure levels.

2.15.3 Human Carcinogenesis Studies

The mutagenic and tumorigenic effects discussed above provide some presumptive evidence for cadmium being a carcinogen in humans. Only a relatively limited number of studies, however, have provided any relevant data on possible cadmium-induced carcinogenicity in humans. Such studies are reviewed in more detail in the later chapter on Human Epidemiology (3.). Therefore, no effort will be made here to review the relevant literature beyond presenting a few summarizing statements and conclusions.

Several epidemiologic studies dealing with increased cancer rates associated with occupational cadmium exposure form a major portion of the existing data base upon which assessments of cadmium-induced human carcinogenicity presently depend. Those studies have previously been evaluated or commented on by other work groups (IARC, 1976; NIOSH, 1976; Carcinogen Assessment Group, 1978; Troast, 1978) and include: The Potts (1965) and Kipling and Waterhouse (1967) studies on the same population of workers exposed to cadmium in a battery manufacturing plant; (2) the study of Lemen et al. (1976) on cadmium-smelter workers; and (3) the study of McMichael et al. (1976) on cadmium-exposed rubber-industry workers.

While the above studies differ in regard to the industrial setting in which cadmium or other possible carcinogens were encountered and vary in their methodological soundness, some striking findings become apparent when their results are summarized together as is done below in Table 2-9. As seen in that table, each study reports increased incidences of various

cancers among the workers studied. Consistent across all of the studies, however, is the finding of higher than normal rates of prostatic cancer. Statistically significant results supporting this were obtained in two of the studies, by Kipling and Waterhouse (1967) and Lemen et al. (1976), while the other two (Potts, 1965, McMichael et al., 1976) reported an apparently high correlation between cadmium exposure and excess prostatic cancer mortality that was not tested by thorough statistical analyses. In each of the above studies, exposure to cadmium oxide occurred as a common element associated with high prostatic cancer rates; highly suggestive evidence, therefore, appears to exist for at least that cadmium salt being carcinogenic in humans with a predilection for the prostate as a site of action. Differences in the findings of increased incidences in other types of cancers among the four studies may, at the same time, indicate that other carcinogenic substances encountered in the work place have sites of predilection that are different from that of cadmium.

Certain "medical geography" studies have been reported (Troast, 1978) as providing additional data linking cadmium exposure to cancer. For example, Berg and Burbank (1972) related incidences of different types of cancers to cadmium levels encountered in water in major water basins of the United States and found that cadmium levels of 3 μg/l (the recommended safety limit is 10 μg/l) were positively correlated with increased incidences of cancer in those geographic areas. These included cancers of the larynx, pharynx, esophagus, intestine, lung, and bladder; but no data on prostatic cancer incidence were reported. Calculations easily demonstrate, however, that the water levels reported in the Berg and Burbank study and usual levels of water consumption are insignificant in comparison to average normal dietary intake (see Chapter 4). Another study (Zyka, 1973) of

Table 2-9. SUMMARY OF RESULTS OF HUMAN EPIDEMIOLOGIC STUDIES OF CANCER EFFECTS ASSOCIATED WITH OCCUPATIONAL EXPOSURES TO CADMIUM

Population group studied	Cadmium compound exposed to	Incidences of all cancers	Incidences of lung cancer	Incidences of Prostate cancer	Reference
Battery factory workers	Cadmium oxide	High	Normal	High	Potts (1965)
Battery factory workers	Cadmium oxide	Normal	Normal	High	Kipling and Waterhouse (1967)
Cadmium Smelter workers	Cadmium oxide, others	High	High	High	Lemen *et al.*, (1976)
Rubber Industry workers	Cadmium oxide	High	Normal	High	McMichael *et al.* (1976)

cadmium in drinking water in Czechoslovakia has been reported (Troast, 1978) as yielding evidence for high levels of trace metals such as cadmium being associated with increased evidences of cancer. Careful inspection of the Zyka (1973) report, however, shows that no association between cadmium and cancer was established (see CAG, 1978).

2.16 INTERACTIONS OF CADMIUM WITH OTHER METABOLIC FACTORS

The extent to which cadmium imparts a toxic effect in man and animals is highly influenced by the status of the organism with reference to a number of essential chemical elements. Scattered throughout the preceding discussion on cadmium's adverse systemic effects are references to the influence of zinc, calcium, and iron. Mention was also made of some of the mechanisms by which these interactions come into play: by metallothionein induction, modification of absorption, etc. Still, it would be appropriate to summarize in a discrete section the nature of these interactions in a general fashion. Recent reviews (Sandstead, 1977; Nordberg, 1976) include a discussion of cadmium-nutrient interactions. Zinc-cadmium relationships have been discussed in considerable detail in the recently published NAS-NRC document, Zinc (1978); in particular, the data from experimental animals have been comprehensively covered.

2.16.1 Zinc

Deficiency of zinc, a nutritionally required metal, increases the toxicity of cadmium. Conversely, increased levels of zinc tend to offset the harmful effects of cadmium.

The protective effect of zinc against testicular necrosis caused by cadmium (Parizek, 1957) was one of the earliest examples of a cadmium-nutrient interaction to be demonstrated. While protection by pretreatment

with zinc would suggest a mechanism involving zinc induction of metallothionein, the cadmium-binding, low-molecular-weight protein; the equal protective efficacy with coadministration of zinc with cadmium would suggest an alternate mechanism, since some induction-time interval would be necessary for metallothionein biosynthesis. Direct zinc-cadmium competition for ligating sites are more plausible in the latter case (Petering, 1971).

A number of studies have indicated that the absolute amounts of either zinc or cadmium are less important than a cadmium/zinc ratio. This certainly appears to be the case with the hypertension experimentally induced by cadmium (see Cardiovascular Effects section). In man, it is known that there is an increase in the cadmium/zinc ratio in hypertensive subjects (Schroeder, 1967; Lener and Bibr, 1971) which probably reflects a loss of zinc. Furthermore, levels of cadmium and zinc in human kidney increase with aging in parallel and in equimolar amounts in the general population (Nordberg, 1976).

The cadmium/zinc relationship may also be synergistic as well as antagonistic in that animal studies on hypertension show both effects appearing across a spectrum of dietary zinc levels (Sanstead, 1976).

2.16.2 Selenium

A number of studies have demonstrated the protective effect of selenium, an essential element, against cadmium toxicity. A demonstration of this element's protective action on cadmium toxicity was the observation of Kar et al. (1960) that co-administration with cadmium prevented testicular necrosis. In addition to testicular protection, selenium abolishes the toxic effects of cadmium on ovaries, placenta, and fetal development. It also elevates the LD_{50} and prevents experimentally induced hypertension in a number of species (Sandstead, 1977; Parizek, 1971).

Several recent studies have been directed toward elucidating the mechanism(s) by which selenium exerts a protective effect. Magos and Webb (1976) studied the effect of co-administration of equimolar amounts of selenium and cadmium parenterally on the transport pattern of either element in adult rats and were led to rule out the *in vivo* formation of cadmium-selenium complexes on a number of grounds, one of which was the cadmium/selenium ratio in kidney.

Gasiewicz and Smith (1976) used ^{75}Se and ^{109}Cd as tracers to study the binding of both elements after simultaneous subcutaneous administration up to 24 hours after injection. Over this time period, the tracers appear in a one-to-one ratio in protein fractions of 130,000 and 330,000 daltons as well as a 420,000-dalton fraction. *In vitro* studies indicate that selenite does not interact directly with cadmium or plasma proteins but is modified to a form that interacts in a one-to-one ratio with cadmium to form a protein complex of 130,000 daltons.

Stowe (1976) studied the effect of selenium on the movement of cadmium through the biliary tract using bile-duct-cannulated rats. Two mg/kg of selenium were given 3 days prior to cadmium administration and following cannulation. There was a significant increase in the biliary excretion of cadmium. Elevated bile levels following selenium pretreatment are consistent with elevated blood cadmium levels and reduced amounts in the liver (Gunn *et al.*, 1968). According to Stowe (1976), it is likely that cadmium present in bile is not associated with metallothionein; but the more unstable, higher molecular-weight fraction which also binds cadmium is stimulated by selenium and is present in testicular tissue (Chen *et al.*, 1974).

Prohaska et al. (1977) studied the relationship in rats among cadmium, selenium, and glutathione peroxidase, a selenoprotein. Rats given a dose of cadmium sufficient to induce a just-visible hemorrhagic response (0.011 mmole/kg, administered subcutaneously) in the testis showed elevated levels of the enzyme. This may be a vasculopathic effect with the increase in activity arising from erythrocyte enzyme via leakage into the testes, enzyme levels in red blood cells being much greater than in testicular tissue. Isolation of the main fractions of the enzyme using labeled cadmium and selenium showed no cadmium-enzyme binding, and these fraction activities were not inhibited by cadmium in vitro. Pretreatment with selenium showed most of the radiolabelled cadmium (^{109}Cd) to be shunted from proteins of low molecular weight (15,000 and 34,000) to a peak with molecular weight 110,000, a selenoprotein. The role of this shifting in testicular protection remains to be demonstrated. Prohaska et al. (1977) found that the postulated role of the cadmium-binding protein of molecular weight 34,000 in testicular injury was not apparent in their animals. Animals not having analyzable protein of this weight sustained testicular injury while older animals showed the protein present with or without concomitant injury. The critical concentration for testicular damage was reported to be 150 nanograms/gram wet weight, above which evidence of injury occurs.

Piotrowski et al. (1977) studied the effect of selenium on cadmium binding to metallothionein. Selenium was found to have little effect on the induction of hepatic metallothionein by cadmium under conditions of repetitive dosing. This may be contrasted to the data of Chen et al. (1975a) who demonstrated an effect in kidney and testes in the direction of higher-weight binding protein.

2.16.3 Calcium

Discussion of a number of interrelationships between calcium and cadmium have been included in other parts of this document, so additional data will be only briefly summarized here.

Calcium deficiency is known to increase the intestinal absorption of cadmium and its subsequent deposition in tissue (Larsson and Piscator, 1971; Itokawa et al., 1974, Pond and Walter, 1975; Washko and Cousins, 1976). Washko and Cousins (1977) found that cadmium retention and signs of toxicity are enhanced by feeding a low calcium diet and that the increased calcium binding protein activity observed is responsible for the increased cadmium uptake. Earlier studies on swine (Hennig and Anke, 1964) and chick (Stancer and Dardzonov, 1967) showed that cadmium has an inhibiting effect on calcium deposition in bone even when calcium is present at normal levels. These doses, however, were extremely high. Data presented in the section on gastrointestinal effects indicate that the absorption effect is imparted in the intestinal epithelium. Effects on Vitamin-D metabolism were discussed in the Sub-Cellular Effects section.

2.16.4 Iron

In the Hematological Effects section it was pointed out that the anemia occasioned by cadmium can be offset by dietary supplementation with ferrous salts.

In the study of Hamilton and Valbert (1974), cadmium fed to rats with restricted iron intake caused a decrease in the uptake of tracer iron (^{59}Fe). As little as 10 ppm cadmium in drinking water had a demonstrable effect, and the data indicate that cadmium competes with iron at one or more steps of iron transport, probably the initial uptake step as shown in

duodenal-perfusion experiments. The effect of cadmium on iron absorption bears important implications for man, since persons with iron deficiency might absorb more cadmium than those with normal iron stores. Flanigan and coworkers (1978) assessed the effect of iron deficiency on increased dietary cadmium in mice and human subjects. Mice fed a low-iron diet and cadmium (10 μM; 1.1 ppm) in drinking water showed impaired growth and accentuated anemia development, while the normal-iron animals showed no effects at the same cadmium-exposure level. Furthermore, the iron deficiency led to increased cadmium levels in the duodenal mucosa and the kidney. In human subjects; experiments using radiolabelled cadmium (^{115m}Cd) showed that individuals with low iron stores absorbed 8.9 μg of 25 μg cadmium given, while the value for individuals with normal iron was 2.3 μg. In human subjects with iron deficiency, an approximate four-fold increase in absorption of cadmium will occur.

2.16.5 Copper

Early evidence for the effect of cadmium on copper metabolism was the observation that dietary cadmium (100 ppm in drinking water) induced aortic morphological abnormalities in chicks which closely resembled the effect of copper deficiency (Hill, 1963). Other effects include the impairment of collagen and elastin linking (Ruchker et al., 1971), a copper-mediated process, and reduction of plasma ceruloplasmin in rats (Campbell and Mills, 1974).

In the study of Irons and Smith (1976), simultaneous administration of copper and cadmium yielded a redistribution of cadmium with little incorporation into metallothionein. This may explain, in part, the synergistic effect of copper when both are given together. The data suggest that retarded incorporation

into metallothionein occurs via copper-mediated aggregation of this protein, an *in vivo* confirmation of demonstrated *in vitro* aggregation (Bremner and Young, 1976).

In contrast, combining copper with zinc and manganese has the joint effect of reducing cadmium accumulation in quail (Fox, 1976).

2.17 REFERENCES FOR CHAPTER 2

Abe, T., S. Tanaka, and Y. Itokawa. Studies on experimental cadmium poisoning. II. Effect of protein and calcium deficiency in chronic cadmium rat poisoning. Nippon Eiseigaku Zasshi 27:308-315, 1972.

Adalis, D., D. E. Gardner, F. J. Miller, and D. L. Coffin. Toxic effects of cadmium on ciliary activity using a tracheal ring system. Environ. Res. 13:111-120, 1977.

Adams, R. G., and N. Crabtree. Anosmia in alkaline battery workers. Br. J. Ind. Med. 18:216-221, 1961.

Alsen, C., C. Kopcke, F. K. Ohnesorge, and J. Schneider. Effects of cadmium on carbonic anhydrase activity and hemoglobin content of rat testes. Arch. Toxicol. 37:39-46, 1976.

Andreuzzi, P., and C. P. Odescalchi. Experimental acute intoxication from cadmium chloride in the rabbit. I. Changes in the GOT-activity in the serum. Boll. Soc. Ital. Biol. Sper. 34:1376-1379, 1976.

Anke, M., A. Hennig; H.-J. Schneider, H. Lüdke, W. von Gagern, and H. Schlegl. The interrelations between cadmium, zinc, copper and iron in metabolism of hens, ruminants and man. In: Trace Element Metabolism in Animals. C. F. Mills (ed.). Livingstone, London, 1970. p. 317.

Axelsson, B., and M. Piscator. Renal damage after prolonged exposure to cadmium. Arch. Environ. Health 12:360-376, 1966.

Baglan, R. J., A. B. Brill, A. Schulert, D. Wilson, K. Larsen, N. Dyer, M. Mansour, W. Schaeffner, L. Hoffman, and J. Davies. Utility of placental tissue as an indicator of trace element exposure to adult and fetus. Environ. Res. 8:64-70, 1974.

Barbieri, L., R. Colombi, and G. Straneo. Modification istologishe delle isole pancreatiche del inconiglio dopo intossicazione crinica da dadmio. Folia Med. 44:1120-1133, 1961.

Barr, M., Jr. The teratogenicity of cadmium chloride in 2 stocks of Wistar rats. Teratology 1:237-242, 1973.

Bauchinger, M., E. Schmid, H. J. Einbrodt, and J. Dresp. Chromosome aberrations in lymphocytes after occupational exposure to lead and cadmium. Mutat. Res. 49:57-62, 1976.

Berg, J. W., and F. Burbank. Correlations between carcinogenic trace metals in water supplies and cancer mortality. Ann. N. Y. Acad. Sci. 199:249-261, 1972.

Berggard, I., and A. G. Beard. Isolation and properties of a low molecular weight β_2-globulin occurring in human biological fluids. J. Biol. Chem. 243(15):4095-4103, 1968.

Berlin, M., and S. Ullberg. The fate of Cd 109 in the mouse. An autoradiographic study after a single injection of Cd 109 Cl_z. Arch. Environ. Health 7:686-693, 1963.

Berliner, A. F., and P. Jones-Witters. Early effects of a lethal cadmium dose on gerbil testes. Biol. Reprod. 13:240-247, 1975.

Bernard, A., H. A. Roels, J. P. Buchet, P. L. Masson, and R. Lauwerys. α_1-antitrypsin level in workers exposed to cadmium. In: Clinical Chemistry and Chemical Toxicology of Metals. S. S. Brown. (ed.). Elsevier, Amsterdam, 1977. p. 161-164.

Berry, J. W., D. W. Osgood, and P. A. St. John. Chemical Villains--A Biology of Pollution. St. Louis, Mo., C. V. Mosby. 1974. 189 p.

Biwas, N. M., S. Chanda, A. Ghosh, and J. Ghakroborty. Effect of cadmium on spermatogenesis in toad (Bufo melanostictus). Endokrinologie 68:(3): 349-352, 1976.

Bremner, I., and J. K. Campbell. The effect of copper and zinc status on susceptibility to cadmium intoxication. Environ. Health Persp. 25:125-128, 1978.

Bremner, I., and B. W. Young. Isolation of (copper, zinc)-thioneines from pig liver. Biochem. J. 155:631, 1976.

Bui, T. H., J. Lindsten, and G. J. Nordberg. Chromosome analysis of lymphocytes from cadmium workers and Itai-Itai patients. Environ. Res. 9:187-195, 1975.

Campbell, J. K., and C. F. Mills. Effects of dietary cadmium and zinc on rats maintained on diets low in copper. Proc. Nutr. Soc. 33:15A-16A, 1974.

Caujolle, F., P. H. Chank, G. Mamy, and L. T. Patle. Comparative action of zinc and cadmium. Agressologie 3:263-268, 1964.

Chandler, J. A., B. G. Timms, M. S. Morton, and G. V. Groom. Proceedings: Effect of cadmium administration in vivo in plasma testosterone and the ultrastructure of accessory sex organs of the rat. J. Endocrinol. 69(3):21P, 1976.

Chatterjee, S. N., and A. B. Kar. Chemical sterilization of stray dogs. Indian Vet. J. 45:649, 1968.

Chaube, S., H. Nishimura, and C. A. Swinyard. Zinc and cadmium in normal human embryos and fetuses. Arch. Environ. Health 26:237-240, 1973.

Chen, R. W., and H. E. Ganther. Some properties of a unique cadmium-binding moiety in the soluble fraction of rat testes. Environ. Physiol. Biochem. 5:235-243, 1975.

Chen, R. W., P. A. Wagner, W. G. Holkstra, and H. E. Ganther. Affinity labelling studies with 109 cadmium in cadmium-induced testicular injury in rats. J. Reprod. Fertil. 38:293-306, 1974

Chen, R. W., P. D. Whanger, and P. H. Weswig. Biological function of metallothionein. I. Synthesis and degradation of rat liver metallothionein. Biochem. Med. 12:95-105, 1975a.

Chen, S. S. Effects of divalent cations and of catecholamines on the late response of the superior cervical ganglion. J. Physiol. 253:443-457, 1975.

Cherian, M. G. Biliary excretion of cadmium in rat. II. The role of metallothionein in the hepatobiliary transport of cadmium. J. Toxicol. Environ. Health 2:955-961, 1977.

Cherian, M. G., and J. J. Vostal. Biliary excretion of cadmium in rat. I. Dose-dependent biliary excretion and the form of cadmium in the bile. J. Toxicol. Environ. Health 2:945-954, 1977.

Cherian, M. G., and Z. A. Shaikh. Metabolism of intravenously injected cadmium-binding protein. Biochem. Biophys. Res. Comm. 65(3):863-869, 1975.

Cherian, M. G., Goyer, R. A., and L. Delaquerriere-Richardson. Cadmium-metallothionein-induced nephropathy. Toxicol. Appl. Pharmacol. 38:399-408, 1975.

Cherian, M. G., R. A. Goyer, and L. Volberg. Gastrointestinal absorption and organ distribution of oral cadmium chloride and cadmium-thionein in mice. Toxicol. Environ. Health 1978. (In press)

Chernoff, N. Teratogenic effects of cadmium in rats. Teratology 8:29-32, 1973.

Chiquoline, A. D. Observations on the early events of cadmium neurosis of the testes. Anat. Rec. 149:23-36, 1964.

Chiquoline, A. D., and V. Suntzeff. Sensitivity of mammals to cadmium neurosis of the testes. J. Reprod. Fertil. 10:455-457, 1965.

Choudhury, H., L. Hastings, G. P. Cooper, and H. G. Petering. Dietary cadmium: Embryotoxicity and neonatal behavioral effects. Annual Report of Center for the Study of the Human Environment. University of Cincinnati. Cincinnati, Ohio, 1977. p. 60.

Chow, C. K., and A. L. Tappel. An enzymatic protective mechanism against lipid peroxidation damage to lungs of ozone-exposed rats. Lipids 1:518-524, 1972.

Chowdhurdy, P., and D. B. Louria. Influence of cadmium and other trace metals on human α-antitrypsin: An *in vitro* study. Science 191:480-481, 1976.

Chowdhurdy, P., and D. B. Louria. Response to Glaser et al. Science 196:556-557, 1977.

Clark, J. N., R. S. Nathaniel, H. K. Kleinman, and G. Wolf. Protein-bound retinol metabolite. Biochem. Biophys. Res. Comm. 62(2):233-240, 1975.

Clegg, E. J., and I. Carr. Changes in the blood vessels of the rat testes and epididymis produced by cadmium chloride. J. Pathol. Bacteriol. 94:317-322, 1967.

Colucci, A. V., D. Winge, and J. Krasno. Cadmium accumulation in rat liver. Arch. Environ. Health 30:153-157, 1975.

Cook, J. A., N. R. DiLuzio, and E. O. Hoffman. Factors modifying susceptibility to bacterial endotoxin: The effect of lead and cadmium. Crit. Rev. Toxicol. 3:201-229, 1975a.

Cook, J. A., E. O. Hoffman, and N. R. DiLuzio. Influence of lead and cadmium on the susceptibility of rats to bacterial challenge. Proc. Soc. Exp. Biol. Med. 150:741-747, 1975b.

Cooper, G. P., and D. Steinberg. Effects of cadmium and lead on adrenergic neuromuscular transmission in the rabbit Am. J. Physiol. 232: C128-C131, 1977.

Costa, B. C., W. J. Pieczynski, N. Janosko, and J. A. Dipaolo. Significance of treatment interval and DNA repair in the enhancement of viral transformation by chemical. Chem. Biol. Interact. 13:105-125, 1976.

Cvetkova, R. P. Materials on the study of the influence of cadmium compounds on the generative function. Gig. Tr. Prof. Zabol. 14:31, 1970.

Deknudt, G., and A. Leonard. Cytogenetic investigations on leucocytes of workers from a cadmium plant. Environ. Physiol. Biochem. 5:319-327, 1975.

Dencker, L. Possible mechanisms of cadmium fetotoxicity in golden hamsters and mice: Uptake by the embryo, placenta and ovary. J. Reprod. Fertil. 44:461-471, 1975.

Der, R. M., Yousef, Z. Fahim, and M. Fahim. Effects of lead and cadmium on adrenal and thyroid functions in rats. Res. Comm. Chem. Pathol. Pharmacol. 17:237-253, 1977a.

Der, R., Z. Fahim, M. Yousef, and M. Fahim. Effects of cadmium on growth, sexual development, and metabolism in female rats. Res. Comm. Chem. Path. Pharmacol. 16(3):485-505, 1977b.

Dixit, V. P., N. K. Lohiya, and M. Agrawal. Effect of cadmium chloride on testis and epididymidis of dog. Acta Biol. Acad. Sci. Hung. 26(1-2): 97-103, 1975.

Dixin, R. L., I. P. Lee, and R. J. Sherins. Methods to assess reproductive effects of environmental chemicals: Studies of cadmium and boron administered orally. Environ. Health Persp. 13:59-67, 1976.

Doyle, J. J., R. A. Benhoft, and H. H. Sandstead. The effects of a low level of dietary cadmium on blood pressure, ^{42}Na, ^{42}K, and water retention in growing rats. J. Lab. Clin. Med. 86:57-63, 1975.

Donnelly, P. A., and D. E. Monty, Jr. Toxicological effects of cadmium chloride on the canine testis following various routes of administration. Toxicol. Lett. 1:53-58, 1977.

Dryden, G. L., and H. Y. McAllister. Sustained fertility after $Cd\ Cl_2$ injection by a non-scrotal mammal, suncus nurinus (Insectivora, Sorcidae). Biol. Reprod. 2:23-30, 1970.

Edstrom, A., and H. Mattson. Inhibition and stimulation of rapid axonal transport *in vitro* by sulfhydryl blockers. Brain Res. 108:381-395, 1976.

Elinder, C.-G., T. Kjellström, L. Friberg, B. Lind, and L. Linnman. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Arch. Environ. Health 31:292-302, 1976.

Elinder, C.-G., T. Kjellström, L. Linnman, and G. Pershagen. Urinary excretion of cadmium and zinc among persons from Sweden. Environ. Res. 15:000-000, 1978.

Epstein, S. S., E. Arnold, J. Andrea, W. Bass, and Y. Bishop. Detection of chemical mutagens by the dominant lethal assay in the mouse. Tox. Appl. Pharm. 23:288-325, 1972.

Eto, K., C. T. G. King, and M. C. Johnston. Developmental effects of teratogens influencing the incidence of cleft lip. J. Dent. Res. 55:B203, 1976.

Evrin, P.-E., and L. Wibell. The serum levels and urinary excretion of β_2-microglobulin in apparently healthy subjects. Scand. J. Clin. Lab. Invest. 29:69-74, 1972.

Exon, J. H., M. M. Patton, and L. D. Koller. Hexamitiasis in cadmium-exposed mice. Arch. Environ. Health 30(9):463-464, 1975.

Faeder, E. J., S. Q. Chaney, L. C. King, T. A. Hunter, R. Bruce, and B. A. Fowler. Biochemical and ultrastructural changes in livers of cadmium-treated rats. Toxicol. Appl. Pharmacol. 39:473-487, 1977.

Favino, A., A. Cavalleri, G. Nazari, and M. Tilli. Testosterone excretion in cadmium chloride induced testicular tumours in rats. Med. Lav. 59:36-40, 1968.

Fende, P. L., and R. J. Niewenhuis. An electron microscopic study of the effects of cadmium chloride on cryptorchid testes of the rat. Biol. Reprod. 16:298-305, 1977.

Ferm, V. H. Developmental malformations induced by cadmium--A study of timed injections during embryogenesis. Biol. Neonate 19:101-107, 1971.

Ferm, V. H., and S. J. Carpenter. The relationship of cadmium and zinc in experimental mammalian teratogenesis. Lab. Invest. 18:429-432, 1968.

Ferm, V. H., D. P. Hanlon, and J. Urban. The permeability of the hamster placenta to radioactive cadmium. J. Embryol. Exp. Morphol. 22:107-113, 1969.

Finlayson, J. S., R. Asofsky, M. Potter and C. C. Runner. Major urinary protein complex of normal micro-origin. Science 149:981-982, 1965.

Flanigan, P. R., J. S. McLellan, J. Haist, M. G. Cherian, M. J. Chamberlain, and L. S. Volberg. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. Gastroenterology. 1978. (In press).

Fleischer, M. A. F. Sarofin, D. W. Fassett, P. Hammand, H. T. Schaklette, I. C. T. Nisbet, and S. Epstein. Environmental impact of cadmium: A review by the panel on hazardous trace substances. Environ. Health Persp. 7:253-323, 1974.

Fleisher, L. N., T. Yorio, and P. J. Bentley. Effect of cadmium on epithelial membranes. Toxicol. Appl. Pharmacol. 33:384-387, 1975.

Flick, D. F., H. F. Kraybill, and J. M. Dimitroff. Toxic effects of cadmium: A review. Environ. Res. 4:71-85, 1971.

Forshaw, P. J. The inhibitory effect of cadmium on neuromuscular transmission in the rat. Europ. J. Pharmacol. 42:371-377, 1977.

Fowler, B. A., H. S. Jones, H. W. Brown, and J. K. Haseman. The morphologic effects of chronic cadmium administration on the renal vasculature of rats given low and normal calcium diets. Toxicol. Appl. Pharmacol. 34:233-252, 1975.

Fox, M. R. S., B. E. Fry, Jr., B. F. Harland, M. E. Schertel, and C. E. Weeks. Effect of ascorbic acid on cadmium toxicity in the young coturnix. J. Nutr. 101:1295-1305, 1971.

Freeland, J. R., and R. J. Cousins. Effect of dietary cadmium on anemia, iron absorption, and cadmium binding protein in the chick. Nutr. Rep. Int. 8:337, 1973.

Friberg, L. Health hazards in the manufacture of alkaline accumulators, with special reference to chronic cadmium poisoning. Acta Med. Scand. Suppl. (40):1-124, 1950.

Friberg, L. Further investigations on chronic cadmium poisoning. AMA Arch. Ind. Hyg. Occup. Med. 5:30-36, 1952.

Friberg, L. Deposition and distribution of cadmium in man in chronic poisoning. Arch. Ind. Health 16:27-29, 1957.

Friberg, L., and E. Odeblad. Localization of Cd^{115} in different organs. An autoradiographic study. Acta Pathol. Microbiol. Scand. 41:96, 1957.

Friberg, L., T. Kjellström, G. Nordberg, and M. Piscator. Cadmium in the Environment-III. A Toxicological and Epidemiological Appraisal. EPA-650/2-75-049, U.S. Environmental Protection Agency, Washington, D.C., 1975.

Friberg, L., M. Piscator, G. F. Nordberg, and T. Kjellström. Cadmium in the Environment. C.R.C. Press. Cleveland, 2nd ed., 1974. p. 248.

Frickenhaus, B., J. Lippal, T. Gordon, and H. J. Einbrodt. Blood pressure and pulse frequency during oral intake of cadmium sulfide in animal experiments. Zentralbl. Bakteriol. Parasitenkd. Infektionser Hyg. Abt. 1: Orig. Reihe B. 161:371-376, 1976.

Fukase, O., and K. Isomura. Effect of metallic cadmium fumes on the peroxidative metabolism of mouse lung. Hyogo-ken Eisei Kenkyusho Kenkyu Hokoku 11:1-3, 1976.

Fulkerson, W., and H. E. Goeller (eds.) Cadmium, the Dissipated Element. ORNL-NSF-EP-21, Oak Ridge National Laboratory, Oak Ridge, Tenn. 1973, p. 473.

Furst, A., and J. D. Mogannam. Inhibition of aryl hydrocarbon hydroxlyase by cadmium ion. Proc. West. Pharmacol. Soc. 18:326-329, 1975.

Gabbiani, G., D. Baic, and C. Deziel. Toxicity of cadmium for the central nervous system. Exp. Neurol. 18:154-160, 1967a.

Gabbiani, G., A. Gregory, and D. Baic. Cadmium-induced selective lesions of sensory ganglia. J. Neuropath. Exp. Neurol. 26(3):498-506.

Gale, T. F. The interaction of mercury with cadmium and zinc in mammalian embryonic development. Environ. Res. 6:95, 1973.

Gale, T. F., and V. H. Ferm. Skeletal malformations resulting from cadmium treatment in the hamster. Biol. Neonate 23:149-160, 1973.

Gardner, D. E., F. J. Miller, J. W. Illing, and J. M. Kirtz. Alterations in bacterial defense mechanisms of the lung induced by inhalation of cadmium. Bull. Europ. Physiopathol. Resp. 13:157-174, 1977.

Gasiewicz, T. A., and J. C. Smith. Interactions of cadmium and selenium in rat plasma *in vivo* and *in vitro*. Biochim. Biophys. Acta 428:113-122, 1976.

Ghafghazi, T., and J. H. Mennear. Effects of acute and subacute cadmium administration on carbohydrate metabolism in mice. Toxicol. Appl. Pharmacol. 26:231-240, 1973.

Ghafghazi, T., and J. H. Mennear. The inhibitory effect of cadmium on the secretory activity of the isolated perfused rat pancreas. Toxicol. Appl. Pharmacol. 31:134-142, 1973.

Gilliavod, N., and A. Leonard. Mutagenicity tests with cadmium in the mouse. Toxicology 5:43-47, 1975.

Girod, C., and M. P. Dubois. Influence d'une injection de clorure de cadmium sur l'axe hypophyso-testiculare du Hamster dore (*Mesocricretus auratus Waterh.*) C. R. Seances Soc. Biol. Ses Fil. 168(8-9):970-974, 1974.

Girod, C., and P. Dubois. Effects of cadmium chloride on the hypophyso-testicular axis of the golden hamster. A study of the antehypophysis with immunofluorescence technique. Ann. Endocrinol. 37:273-274, 1976.

Glaser, C. B., L. Laric, T. Huffaker, and R. J. Fallat. Influence of cadmium on human alpha-1-antitrypsin: A re-examination. Science 196:556-557, 1977.

Gleason, M. N., R. E. Gosselin, I. C. Hodge, and R. P. Smith. Clinical Toxicology of Commercial Products, 3rd Ed. Williams and Wilkins, Baltimore, 1969. p. 51.

Gonick, H., S. Indraprasit, H. Neustein, and V. Rosen. Cadmium-induced experimental Fanconi syndrome. Curr. Probl. Clin. Biochem. 4:111-118, 1975.

Graham, J. A., D. E. Gardner, M. E. Waters, and D. L. Coffin. Effect of trace minerals on phagocytosis by alveolar macrophages. Infect Immunun. 1I(6):1278-1283, 1975.

Gunn, S. A., and T. C. Gould. Cadmium and other mineral elements. In: The Testes. A. D. Johnson, W. R. Games, and N. L. VanDemark (eds.). Academic Press, New York, 1970. p. 377.

Gunn, S., T. Gould, and W. Anderson. Zinc protection against cadmium injury to rat testes. Arch. Pathol. 71:52-57, 1961.

Gunn, S. A., T. C. Gould, and W. A. D. Anderson. Cadmium-induced interstitial cell tumors in rats and mice and their prevention by zinc. J. Natl. Cancer Inst. 31:745-759, 1963.

Gunn, S. A., T. C. Gould, and W. A. D. Anderson. Effect of zinc on cancerogenesis by cadmium. Proc. Soc. Exp. Biol. Med. 115:653-657, 1964.

Gunn, S. A., T. C. Gould, and W. A. D. Anderson. Comparative study of interstitial cell tumors of rat testis induced by cadmium injection and vascular ligation. J. Natl. Cancer Inst. 35:329-337, 1965.

Gunn, S. A., T. C. Gould, and W. A. D. Anderson. Specific response of mesenchymal tissue to carcinogenesis by cadmium. Arch. Path. 83:493-499, 1967.

Gunn, S. A., T. C. Gould, and W. A. D. Anderson. Mechanisms of zinc, cysteine and selenium protection against cadmium-induced vascular injury to mouse testes. J. Reprod. Fertil. 15:65-70, 1968.

Guthrie, J. Histological effects of intra-testicular injections on cadmium chloride in domestic fowl. Br. J. Cancer 18:256-260, 1964.

Haddow, A., F. J. C. Roe, C. E. Dukes, and B. C. V. Mitchley. Cadmium neoplasia: Sarcomata at the site of injection of cadmium sulphate in rats and mice. Br. J. Cancer 18:667-673, 1964.

Hamilton, D. L., and L. S. Valberg. Relationship between cadmium and iron absorption. Am. J. Physiol. 227:1033-1037, 1974.

Hart, D. T., and J. L. Borowitz. Adrenal catecholamine release by divalent mercury and cadmium. Arch. Int. Pharmacodyn. Ther. 209:94-99, 1974.

Hayes, J. A., G. L. Snider, and K. C. Palmer. The evolution of biochemical damage in the rat lung after acute cadmium exposure. Am. Rev. Resp. Dis. 113:121-130, 1976.

Heath, J. C., and M. R. Daniel. The production of malignant tumours by cadmium in the rat. Br. J. Cancer. 18:124-129, 1964.

Heath, J. C., M. R. Daniel, J. T. Dingle, and M. Webb. Cadmium as a carcinogen. Nature 193:592-593, 1962.

Hennig, A., and M. Anke. Arch. Tiereraehr 14:55-57, 1964.

Hidalgo, H. A., and S. E. Bryan. Cadmium-115 bound to nuclear and cytoplasmic proteins. Toxicol. Appl. Pharmacol. 42:319-327, 1977.

Hill, C. H., G. Natrone, W. L. Payne, and C. W. Barber. J. Nutr. 80:227-235, 1963.

Hrdina, P. D., D. A. V. Peters, and R. L. Singhal. Effects of chronic exposure to cadmium, lead and mercury on brain biogenic amines in the rat. Res. Comm. Chem. Path. Pharmacol. 15(3):483-493, 1976.

Hurley, L. S., and H. Sweneston. Congenital malformations resulting from zinc deficiency in rats. Proc. Soc. Exp. Biol. Med. 123:692, 1966.

Hurley, L. S., J. Gowan, and H. Sweneston. Teratogenic effects of short-term and transitory zinc deficiency in rats. Teratology 4:199, 1971.

International Agency for Research on Cancer. Cadmium and Cadmium Compounds. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anesthetics. Vol. II. International Agency for Research on Cancer, Lyon, France. 1976. p. 40-75.

Iqbal, M., J. P. Waterhouse, and M. R. Cheda. Cadmium effect on phosphatases in salivary glands, kidney and intestines. J. Dent. Res. 55:B183, 1976.

Irons, R. D., and J. C. Smith. Prevention by copper of cadmium sequestration by metallothionein in liver. Chem. Biol. Interact. 15:289-294, 1976.

Ishizaki, A., M. Fukushima, and M. Sakamoto. On the accumulation of cadmium in the bodies of Itai-Itai patients. Nippon Eiseigaku Zaashi 25:86, 1970.

Ishizu, S., M. Minami, A. Suzuki, M. Yamada, M. Sato, and K. Yamamura. An experimental study on teratogenic effects of cadmium. Ind. Health 11:127-139, 1973.

Ithakissios, P. S., J. Ghafghazi, J. H. Mennea, and W. V. Kessler. Effect of multiple doses of cadmium on glucose metabolism and insulin secretion in the rat. Toxicol. Appl. Pharmacol. 31:143-149, 1975.

Itokawa, Y., T. Abe, R. Tabei, and S. Tanaka. Renal and skeletal lesions in experimental cadmium poisoning. Arch. Environ. Health 28:149-154, 1974.

Johanson, B. G., and U. Ravnskov. The serum level and urinary excretion of α_2-microglobulin, β_2-microglobulin and lysozyme in renal disease. Scand. J. Urol. Nephrol. 6:249-256, 1972.

Johnson, A. D., and G. P. Walker. Early actions of cadmium in the rat and domestic fowl testes: V. Inhibition of carbonic anhydrase. J. Reprod. Fertil. 23:463-468, 1970.

Johnson, A. D., W. R. Gomes, and N. L. Demark. Early actions of cadmium in the rat and domestic fowl testes: I. Testes and body temperature changes caused by cadmium and zinc. J. Reprod. Fertil. 21:383-393, 1970.

Johnson, D. E., R. J. Prevost, J. B. Tillery, and R. E. Thomas. The Distribution of Cadmium and Other Metals in Human Tissue. Final Report, Contract No. 68-02-1725. Prepared by Southwest Research Institute, San Antonio, Texas, for U.S. Environmental Protection Agency, Washington, D.C. 1977.

Kacew, S., Z. Merali, A. N. Thakur, and R. L. Singhal. Sequential changes in hepatic polyamine, deoxyribonucleic acid, and cyclic adenosine 3'5'-monophosphate metabolism after subacute exposure to cadmium in rats. Can. J. Physiol. Pharmacol. 55:508-514, 1977.

Kamata, T., N. Sato, T. Suematsu, F. Furuyama, and B. Ogihara. Biochemistry of the biological protection reaction. The effect of cadmium on the function of mitochondria of the rat liver. Igaku No Ayumi 96(7):503-504, 1976.

Kamino, K., N. Uyesaka, M. Ogawa, and A. Inouye. Cadmium-binding of synaptosomes isolated from rat brain cortex. J. Membr. Biol. 21:113-124, 1975.

Kanisawa, M., and H. A. Schroeder. Life term studies on the effects of trace elements on spontaneous tumors in mice and rats. Cancer Res. 29:892-895, 1969.

Kar, A. B. Chemical sterilization of male Rhesus monkeys. Endocrinology 69:1116-1119, 1961.

Kar, A. B., and R. P. Das. Testicular changes in rat after treatment with cadmium chloride. Acta Biol. Med. Ger. 5:153-173, 1960.

Kar, A. B., and R. P. Das. Sterilization of males by intratesticular administration of cadmium chloride. Acta Endocrinol. 40:321, 1962.

Kar, A., R. Das, and J. Karukun. Ovarian changes in prepubertal rats after treatment with cadmium chloride. Acta Biol. Med. Ger. 3:372-399, 1959.

Kar, A. B., R. P. Das, and B. Mjkerji. Prevention of cadmium-induced changes in the gonads of rat by zinc and selenium--A study in antagonism between metals in the biological system. Proc. Natl. Inst. Sci. 26:40, 1960.

Kasuya, M., N. Sugawara, and A. Okada. Toxic effect of cadmium stearate on rat cerebellum in culture. Bull. Environ. Contam. Toxicol. 12:535-540, 1974.

Kaul, D. K., and L. S. Ramaswami. Effect of cadmium chloride on the ovary of the Indian desert gerbil, Merionis hurrianae Jerdon. Indian J. Exp. Biol. 8:171-173, 1970.

Kawahara, H., Y. Takashima, M. Nakamura, and A. Yamagami. Electron microscopic study of the cytotoxicity of cadmium and mercury in vitro. J. Dent. Res. 54:125-130, 1975.

Kawai, K., and K. Fukuda. Pathological findings in experimental cadmium poisoning. In: Materials of the Research Meeting Concerning Cadmium Poisoning. Japanese Association of Public Health, March 16, 1974. p. 29-30.

Kawai, K., K. Fukuda, and M. Kimura. Morphological alterations in experimental cadmium exposure. Paper presented at the 3rd Meeting of the Subcommittee on the Toxicology of Metals, Tokyo, 1974.

Kawai, K., K. Fukuda, and M. Kimura. Morphological alterations in experimental cadmium exposure with special reference to the onset of renal lesion. In: Effects and Dose-Response Relationships of Toxic Metals. G. F. Nordberg (ed.). Elsevier, Amsterdam, 1976. p. 343-370.

Kanai, M., S. Nomoto, S. Sasaoka, and M. Naiki. Clinical significance of urinary excretion of retinol-binding protein in patients with Itai-Itai disease. Rinsho Kagaku Shimpojumu 11:194-199, 1971.

Kanai, M., S. Nomoto, S. Sasaoka, and Y. Muto. Retinol-binding protein levels in blood and urine from patients with Itai-Itai disease: pathological mechanism for its increased excretion. Rinsho Kagaku Shimpojumu 12:319-324, 1972.

Kazantzis, G. Induction of sarcoma in the rat by cadmium sulphide pigment. Nature 198:1213-1214, 1963.

Kazantzis, G., and W. J. Hanbury. The induction of sarcoma in the rat by cadmium sulphide and by cadmium oxide. Br. J. Cancer. 20:190-199, 1966.

Kimura, M., and N. Otaki. Percutaneous absorption of cadmium in rabbit and hairless mouse. Ind. Health 10:7-10, 1972.

Kipling, M. D., and J. A. H. Waterhouse. Cadmium and prostatic cancer. Lancet 1:730-731, 1967.

Kjellström, T. A mathematical model for the accumulation of cadmium in humans. Nord. Hyg. Tidskr. 53:111-119, 1971.

Kjellström, T., and M. Piscator. β_2-microglobulin in urine induced by cadmium. Phaldoc: Diag. Comm.: No. 1. Uppsala, Sweden, Pharmacia Diagnostics AB. 1977. p. 21.

Kjellström, T., P.-E. Evrin, and B. Rahnster. Dose-response relationship of cadmium-induced tubular proteinuria. A study of workers exposed to cadmium in a Swedish battery factory. Environ. Res. 13:303-317, 1977a.

Kjellström, T., K. Shiroishi, and P.-E. Evrin. Urinary β_2-microglobulin excretion among people exposed to cadmium in the general environment. Environ. Res. 13:318-344, 1977b.

Knorre, K. Ortliche Hautschadigungen an der Albinoratte in der Latenzperiode der Sarkomentwicklung nach Kadmiumchloridinjection. Zentralbl. Allg. Pathol. Pathol. Anat. 113:192-197, 1970.

Knorre, D. Zur Induktion von Hodenzwischenzelltumoren an der Albinoratte durche Kadmiumchlorid. Arch. Geschwulstforsch. 38:257-263, 1971.

Kojima, S., Y. Haza, T. Kurihara, T. Tamawaki, and T. Kjellström. A comparison between fecal cadmium and urinary β_2-microglobulin, total protein, and cadmium among Japanese farmers. Environ. Res. 14(3):436-451, 1977.

Koller, L. Immunosuppression produced by lead, cadmium and mercury. Am. J. Vet. Res. 34:1457-1458, 1973.

Koller, L. D., and J. G. Roan. Effects of lead and cadmium on mouse peritoneal macrophages. Res J. Reticuloendathel. Soc. 21:7-12, 1977.

Koller, L. D., J. H. Exon, and J. G. Roan. Antibody suppression by cadmium. Arch. Environ. Health 30:598-601, 1975.

Kopp, S. J., H. M. Perry, Jr., V. W. Fischer, M. W. Erlanger, and E. F. Perry. Altered myocardial excitability, morphology, and metabolism induced by long-term, low level cadmium feeding. Trace Substances in Environmental Health. Proceedings of Univ. of Missouri 12th Annual Conference (in press).

Koskimies, A. I. Effect of cadmium on protein composition of fluids in rat testes and seminiferous tubules. Ann. Med. Exp. Biol. Fenn. 51:74-81, 1973.

Krasny, H. C., and D. J. Holbrook, Jr. Effects on microsomal hemoproteins and heme oxygenase in rat liver. Mol. Pharmacol. 13:759-765, 1977.

Krasovskii, G. N., S. P. Varshavskaya, and A. I. Borisov. Toxic and gonadotropic effects of cadmium and boron relative to standards for these substances in drinking water. Environ. Health Persp. 13:69-75, 1976.

Larsson, S., and M. Piscator. Effect of cadmium on skeletal tissue in normal and cadmium-deficient rats. Isr. J. Med. Sci. 7:495, 1971.

Lauwerys, R., R. J. Bucket, H. A. Roels, J. Brouwers, and D. Staneschu. Epidemiological survey of workers exposed to cadmium. Arch. Environ. Health 28:145-148, 1974.

Leber, A. P., and T. S. Miya. A mechanism for cadmium-and zinc-induced tolerance to cadmium toxicity: Involvement of metallothionein. Toxicol. Appl. Pharmacol. 37:403-414, 1976.

Lemen, R. A., J. S. Lee, J. K. Wagoner, and H. P. Blejer. Mortality among cadmium production workers. Ann. N. Y. Acad. Sci. 271:273-279, 1976.

Lener, J., and B. Bibr. Cadmium and hypertension. Lancet 1:970, 1971.

Leslie, S. W., and J. L. Borowitz. Inhibition of the adrenal chromaffin cell membrane calcium pump by caffeine and various divalent cations. Res. Comm. Chem. Pathol. Pharmacol. 11:413-424, 1975.

Levy, L. S., and J. Clack. Further studies on the effect of cadmium on the prostate gland--I. Absence of prostatic changes in rats given oral cadmium sulphate for two years. Ann. Occup. Hyg. 17:205-211, 1975.

Levy, L. S., D. Clack, and F. J. C. Roe. Further studies on the effect of cadmium on the prostate gland-II. Absence of prostatic changes in mice given oral cadmium sulfate for eighteen months. Ann. Occup. Hyg. 17:213-220, 1975.

Levy, L. S., F. J. C. Roe, D. Malcolm, G. Kozantzis, J. Clack, and H. S. Platt. Absences of prostatic changes in rats exposed to cadmium. Ann. Occup. Hyg. 16:111-118, 1973.

Loeser, E., and D. Lorke. Semichronic oral toxicity of cadmium. I. Studies on rats. Toxicology 7:215-224, 1977a.

Loeser, E., and D. Lorke. Semichronic oral toxicity of cadmium. II. Studies on dogs. Toxicology 7:225-232, 1977b.

Loose, L. D., J. B. Silkworth, and D. Warrington. Cadmium-induced depression of the respiratory burst in mouse. Pulmonary alveolar macrophages, peritoneal macrophages and polymorphonuclear neutrophils. Biochem. Biophys. Res. Comm. 79:326-332, 1977.

Lorentzon, R., and S. E. Larsson. Vitamin D metabolism in adult rats at low and normal calcium intake and the effect of cadmium exposure. Clin. Sci. Mol. Med. 53:439-446, 1977.

Lucis, O. J., R. Lucis, and K. Aerman. The transfer of 109-cadmium and 65-zinc from the mother to the newborn rat. Fed. Proc. Fed. Am. Soc. Exp. Biol. 30: 238, 1971.

Lucis, O. J., Lucis, R., and K. Aterman. Tumorigenesis by cadmium. Oncology 26:53-67, 1972.

Lynch, G. P., D. F. Smith, M. Fisher, T. L. Pike, and B. T. Weinland. Physiological responses of calves to cadmium and lead. J. Anim. Sci. 42:410-421, 1976.

Maekawa, K., and Y. Tounenari. Mechanism involved in selective injurious effect of cadmium on the testis. Gunma Symp. Endocrinol. 4:161-1967.

Maekawa, K., T. Suzuki, and Y. Teunenari. Damage of the gonads induced by cadmium in male and female ring doves (Streptopelia risoria). Kaibogaku Zasshi 39:291-301, 1964.

Magos, L., and M. Webb. Differences in destruction and excretion of selenium and cadmium or mercury after their simultaneous administration subcutaneously in equimolar doses. Arch. Toxicol. 36:63-69, 1976.

Maji, T., and A. Yoshida. Therapeutic effect of dietary iron and ascorbic acid on cadmium toxicity of rats. Nutr. Rep. Int. 10(3):139-149, 1974.

Mason, K. E., J. A. Brown, J. P. Young, and R. R. Nesbitt. Cadmium-induced injury of the rat testes. Anat. Rec. 149:135-148, 1964.

McMichael, A. J., D. A. Andjelkovic, and H. A. Tyroler. Mortality among rubber workers: An epidemiologic study. Ann. N. Y. Acad. Sci. 271: 124-137, 1976.

Mego, J. L., and J. A. Cain. An effect of cadmium on heterolysosome formation and function in mice. Biochem. Pharmacol. 24:1227-1232, 1975.

Merali, Z., and R. L. Singhal. Protective effect of selenium on certain hepatotoxic and pancreotoxic manifestations of subacute cadmium administration. J. Pharmacol. Exp. Ther. 195:58-66, 1975.

Miller, M. L., Murthy, and J. R. Sorenson. Fine structure of connective tissue after ingestion of cadmium. Arch. Pathol. 98:386-392, 1975.

Mulvahill, J. E., S. H. Gamm, and V. H. Ferm. Facial formation in normal and cadmium treated golden hamsters. J. Embryol. Exp. Morphol. 24:393-403, 1970.

Murata, I., J. Hirono, Y. Saeki, and W. S. Nakaga. Cadmium enteropathy, renal osteomalacia ("Itai-Itai" disease in Japan). Bull. Soc. Int. Chir. 29:34-42, 1970.

Murthy, L., J. R. J. Sorenson, and H. G. Petering. Effect of cadmium on ceruloplasmin (copper oxidase) activity in rats. Fed. Proc. Fed. Am. Soc. Exp. Biol. Proc. 56th Ann. Meeting of American Societies for Experimental Biology, 1972. Abstr #2726. p. 669 abs 1972.

Muto, Y., M. Nakanishi, and Y. Shidoji. Urinary excretion of retinol-binding protein (RBP) in rabbit chronically poisoned with cadmium. Isolation and partial characterization of rabbit RBP. J. Biochem. 79:775-785, 1976.

Nathanson, J. A., and F. E. Bloom. Heavy metals and adenosine cyclic 3',5'-monophosphate metabolism: Possible relevance to heavy metal toxicity. Mol. Pharmacol. 12:390-398, 1976.

National Academy of Sciences. Zinc. EPA-600/1-78-034, U.S. Environmental Protection Agency. Washington, D.C., May, 1978.

National Institute for Occupational Safety and Health. Criteria for a Recommended Standard. Occupational Exposure to Cadmium. HEW Publication No. (NIOSH) 76-192. U.S. Department of Health Education and Welfare, Public Health Service, Center for Disease Control, Cincinnati, Ohio, August, 1976.

Nazari, G., A. Favino, and U. Pozzi. Effetti di un'unica iniezione sottocutanea di cadmio cloruro nel ratto maschio. Riv. Anat. Pathol. Oncol. 31:251-270, 1967.

Nechay, B. R., and J. P. Saunders. Inhibition of renal adenosine triphosphatase by cadmium. J. Pharmacol. Exp. Ther. 200:623-629, 1977.

Neigi, G., J. P. Berry, P. Galle, J. Ripault, H. Desoille, and M. Philbert. Appearance of cytotoxic hepatic lesions during experimental cadmium intoxication. Arch. Mol. Prof. Med. Trav. Secur. Soc. 35:709-718, 1974.

Nicand, O., A. Lafitte, and A. Gros. Arch. Mal. Prof. Med. Trav. Secur. Soc. 4:192, 1942.

Nishioka, H. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31:185-189, 1975.

Nomiyama, K. Studies concerning cadmium metabolism and the etiology of poisoning. Toxicol. Appl. Pharmacol. 31:4-12, 1975.

Nordberg, G. F. Effects of acute and chronic cadmium exposure on the testicles of mice, with special reference to the protective effects of metallothionein. Environ. Physiol. Biochem. 1:171-187, 1971.

Nordberg, G. F. Cadmium metabolism and toxicity. Experimental studies on mice with special reference to the use of biological materials as indices of retention and the possible role of metallothionein in transport and detoxification of cadmium. Environ. Physiol. Biochem. 2:7-36, 1972.

Nordberg, G. F. Health hazards of environmental cadmium pollution. Ambio 3:55-66, 1974.

Nordberg, G. F. Effects of long-term cadmium exposure on the seminal vesicles of mice. J. Reprod. Fertil. 45:165-167, 1975.

Nordberg, G. F. (ed.). Effects and Dose-Response Relationships of Heavy Metals. Elsevier, Amsterdam. 1976.

Nordberg, G. F., and K. Nishiyama. Whole-body and hair retention of cadmium in mice. Arch. Environ. Health 24:209-214, 1972.

Nordberg, G. F., and M. Piscator. Influence of long-term cadmium exposure on urinary excretion of protein and cadmium in mice. Environ. Physiol. Biochem. 2:37, 1972.

Nordberg, M., and G. F. Nordberg. Distribution of metallothionein-bound cadmium and cadmium chloride in mice. Preliminary studies. Environ. Health Persp. 12:103-108, 1975.

Norton, K. B., and J. E. Kench. Effects of cadmium on ribosomal protein synthesis in rat liver. Environ. Res. 13:102-110, 1977.

O'Dell, B. D., D. W. Bird, D. L. Ruggles, and J. E. Savage. Composition of aortic tissue from copper deficient chicks. J. Nutr. 88:9-14, 1966.

Ogawa, E., S. Suzuki, H. Tauzuki, and M. Kawajiri. Basal study on early diagnosis of cadmium poisoning: Change in carbonic anhydrase activity. Jpn. J. Pharmacol. 23:97-105, 1973.

Omaye, S. J., and A. L. Tappel. Effect of cadmium chloride on the rat testicular soluble selenoenzyme, glutathione peroxidase. Res. Comm. Chem. Pathol. Pharmacol. 12:695-711, 1975.

Ozawa, K., A. Sato, and H. Okada. Differential susceptibility of L cells in the exponential and stationary phases to cadmium chloride. Jpn. J. Pharmacol. 26:347-351, 1976.

Parizek, J. The destructive effect of cadmium ion on testicular tissue and its prevention by zinc. J. Endocrinol. 15:56-63, 1957.

Parizek, J. Sterilization of the male by cadmium salts. J. Reprod. Fertil. 1:294-309, 1960.

Parizek, J. Vascular changes at sites of estrogen biosynthesis produced by parenteral injection of cadmium salts - The destruction of the placenta by cadmium salts. J. Reprod. Fertil. 7:263-265, 1964.

Parizek, J. The detoxifying effects of selenium: Inter-relations between compounds of selenium and certain metals. In: Newer Trace Elements in Nutrition. W. Meltz and W. E. Cornatzer. (eds.). Dekker, New York, 1971. p. 85-122.

Parizek, J., and Z. Zahor. Effect of cadmium salts on testicular tissue. Nature 177:1036-1037, 1956.

Parizek, J., I. Ostadalova, L. Benes, and A. Babicky. Pregnancy and trace elements - The protective effect of compounds of an essential trace element - selenium - against the peculiar toxic effects of cadmium during pregnancy. J. Reprod. Fertil. 16:507-509, 1968.

Patwardhan, J. R., and E. S. Finckh. Fatal cadmium-fume pneumonitis. Med. J. Austral. 1:962-966, 1976.

Perry, H. M., Jr. Review of hypertension induced in animals by chronic ingestion of cadmium. In: Trace Elements in Human Health and Disease, Vol. 2. Essential and toxic Elements. A. S. Prasad and D. Oberleas (ed.). Academic Press, New York, 1976. p. 417-430.

Perry, H. M., Jr., and M. W. Erlanger. Hypertension in rats induced by long-term low-level cadmium ingestion. Circulation Suppl 44:130, 1971.

Perry, H. M., Jr., and M. Erlanger. Hypertension and tissue metal levels after intraperitoneal cadmium, mercury, and zinc administration. Am. J. Physiol. 220:808-811, 1971.

Perry, H. M., Jr., and M. Erlanger. Elevated circulating renin activity in rats following doses of cadmium known to induce hypertension. J. Lab. Clin. Med. 82:399-405, 1973.

Perry, H. M., Jr., and M. W. Erlanger. Metal-induced hypertension following chronic feeding of low doses of cadmium and mercury. J. Lab. Clin. Med. 83:541-547, 1974.

Perry, H. M., Jr., and E. F. Perry. Metals and human hypertension. Epidemiology and control of hypertension. Discussion from the 2nd Intl. Symp. on the Epidemiology of Hypertension, September, 1974. Symposia Specialist Medical Books, Miami, 1975. p. 147-162.

Perry, H. M., Jr., M. Erlanger, and E. F. Perry. Elevated systolic pressure following chronic low-level cadmium feeding. Am. J. Physiol. 232:H114-H121, 1977a.

Perry, H. M., Jr., M. W. Erlanger, and E. F. Perry. Hypertension following chronic, very low dose cadmium feeding. Proc. Soc. Exp. Biol. Med. 156:173-176, 1977b.

Perry, H. M., Jr., and M. W. Erlanger. Marked increases in rat systolic pressure following very low but prolonged cadmium feeding. Fed. Proc. Fed. Am. Soc. Exp. Biol. 37:294, 1978.

Petering, H. G., Johnson, M. A., and Stemmer, K. L. Studies of zinc metabolism in the rat. Arch. Environ. Health 23:93, 1971.

Peterson, P. A., and I. Berggard. Isolation and properties of a human retinol-transporting protein. J. Biol. Chem. 246(1):25-33, 1971.

Pierce, R. J., R. G. Price, and J. S. L. Fowler. The effect of cadmium administration on activities of enzymes in the urine of the rat and marmoset. Biochem. Soc. Trans. 5:238-241, 1977.

Pierro, L. J., and J. S. Haines. Cd-induced exencephaly and eye defects in the mouse. Teratology 13:33A, 1976.

Pihl, R. O., and M. Parkes. Hair element content in learning disabled children. Science 198:204-206, 1977.

Piotrowski, J. K., E. M. Ben, and A. Werner. Cadmium and mercury binding to metallothionein as influenced by selenium. Biochem. Pharmacol. 26:2191-2192, 1977.

Piscator, M. On cadmium in normal human kidneys together with a report on the isolation of metallothionein from livers of cadmium-exposed rabbits. Nord. Hyg. Tidskr. 415:76-86, 1964.

Piscator, M. Proteinuria in Chronic Cadmium Poisoning. Beckmans, Stockholm, 1966a.

Piscator, M. Proteinuria in chronic cadmium poisoning. III. Electrophoretic and immunoelectrophoretic studies on urinary protein from cadmium workers, with special reference to the excretion of low molecular weight proteins. Arch. Environ. Health 12:335-344, 1966b.

Piscator, M. Proteinuria in chronic cadmium poisoning. IV. Gel filtration and ion exchange chromatography of urinary proteins from cadmium workers. Arch. Environ. Health 12:345-359, 1966c.

Piscator, M., and B. Axelsson. Serum proteins and kidney function after exposure to cadmium. Arch. Environ. Health 21:604-608, 1970.

Pond, W. G., and E. F. Walker, Jr. Cadmium-induced amino in growing rats: Prevention by oral or parenteral iron. Nutr. Rep. Int. 5(6):365-370, 1972.

Pond, W. G., and E. F. Walker, Jr. Effect of dietary Ca and Cd level of pregnant rats on reproduction and on dam and progeny tissue mineral concentrations. Proc. Soc. Exp. Biol. Med. 148:665-668, 1975.

Popham, J. D., and W. S. Webster. The ultrastructural localization of cadmium. Histochemistry 46:249-259, 1976.

Porter, M. C., T. S. Miya, and W. F. Bousquet. Cadmium and vascular reactivity in the rat. Toxicol. Appl. Pharmacol. 34:143-150, 1975.

Potts, C. L. Cadmium proteinuria - The health of battery workers exposed to cadmium oxide dust. Ann. Occup. Hyg. 8:55-61, 1965.

Prigge, E., H. P. Baumert, and H. Muhle. Effects of dietary and inhalative cadmium on hemoglobin and hematocrit in rats. Bull. Environ. Contam. Toxicol. 17:585-590, 1977.

Probst, G. S., W. F. Bousquet, and T. S. Miya. Correlation of hepatic metallothionein concentrations with acute cadmium toxicity in the mouse. Toxicol. Appl. Pharmacol. 39:61-69, 1977.

Prohoska, J. R., M. Mowafy, and H. E. Ganther. Interactions between cadmium, selenium, and glutathione reductase in rat testes. Chem. Biol. Interact. 18:253-265, 1977.

Ramaswami, L. S., and D. K. Kaul. The effect of cadmium and selenium on the testis of the desert gerbil (Meriones hurrianae Jerdon). J. R. Microscop. Soc. 85:297, 1966.

Rastogi, R. B., and R. L. Singhal. Effect of chronic cadmium treatment on rat adrenal catecholamines. Endocr. Res. Commun. 2:87-94, 1975.

Ray, P., and A. Chatterjee. Reserpine, adrenalectomy, and the reversal of the early action of cadmium on scrotal and cryptorchid testes in the rat. J. Reprod. Fertil. 33:523-526, 1973.

Reddy, J., D. Svoboda, D. Azarnoff, and R. Dawas. Cadmium-induced Leydig cell tumors of rat testis: Morphological and cytochemical study. J. Natl. Cancer Inst. 51:891-903, 1973.

Ribas-Ozonas, B., M. C. O. Estomba, and A. Santos-Ruiz. Activation of serotonin and 5-hydroxyindoleacetic acid in brain structures after application of cadmium. In: Trace Element Metabolism in Animals. W. G. Hoikstra, J. W. Suttie, H. E. Ganther, and W. Mertz (eds.). University Park Press, Baltimore, 1974. p. 476-478.

Richardson, M. E., and M. R. S. Fox. Dietary cadmium and enteropathy in the Japanese quail. Lab. Invest. 31:722-731, 1974.

Richardson, M. E., M. R. S. Fox, and B. E. Fry, Jr. Pathological changes produced in Japanese quail by ingestion of cadmium. J. Nutr. 104(3):323-388, 1974.

Roe, F. J. C., C. E. Dukes, K. M. Cameron, R. C. B. Pugh, and B. C. V. Mitchley. Cadmium neoplasia: Testicular atrophy and Leydig cell hyperplasia and neoplasia in rats and mice following the subcutaneous injection of cadmium salts. Br. J. Cancer 18:674-681, 1964.

Roels, H. A., J. P. Buchet, R. R. Lauwerys, and J. Sonnet. Comparison of *in vivo* effect of inorganic lead and cadmium on glutathione reductase system and δ-aminolevulinate dehydratase in human erythrocytes. Br. J. Ind. Med. 32:181-192, 1975.

Rucker, R. B., B. L. O'Dell, H. E. Parker, and J. D. Rogler. The role of copper in the crosslinking of collagen and elastin. *In*: Trace Substances in Environmental Health-IV. D. D. Hemphill (ed.). University of Missouri Press, Columbia, Mo., 1971. p. 255-259.

Saksena, S. K., L. Dahlgren, I. F. Lau, and M. C. Chang. Reproductive and endocrinological features of male rats after treatment with cadmium chloride. Biol. Reprod. 16:609-613, 1977.

Sandstead, H. H. Interactions of cadmium and lead with essential minerals. *In*: Effects and Dose-Response Relationships of Toxic Metals. G. F. Nordberg (ed.). Elsevier, Amsterdam, 1976. p. 510-526.

Sangalang, G. B., and M. J. O'Halloran. Cadmium-induced testicular injury and alterations of androgen synthesis in brook trout. Nature 240:470-471, 1972.

Sarkar, A. K., and R. Mondal. Injurious effect of cadmium on testis of domestic pigeon and its prevention by zinc. Indian J. Exp. Biol. 11:108-109, 1972.

Schlaepfer, W. W. Sequential study of endothelial changes in acute cadmium intoxication. Lab. Invest. 25(6):556-564, 1971.

Schroeder, H. A. Cadmium, chromium, and cardiovascular disease. Circulation 35(3):570-582, 1967.

Schroeder, H. A., and M. Mitchener. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health. 23:102-106, 1971.

Schroeder, H. A., and E. H. Vinton, Jr. Hypertension induced in rats by small doses of cadmium. Am. J. Physiol. 202:515-518, 1962.

Schroeder, H. A., J. J. Balassa, and W. H. Vinton, Jr. Chronic cadmium and lead in rats--Effects on life span, tumors and tissue levels. J. Nutr. 86:51-66, 1965.

Schroeder, H. A., S. S. Kroll, J. W. Little, P. O. Livingstone, and M. A. G. Myers. Hypertension in rats from injection of cadmium. Arch. Environ. Health 13:778-780, 1967.

Semba, R., K. Ohta, and H. Yamamura. Low-dose preadministration of cadmium prevents cadmium-induced exencephalia. Teratology 10:96-97, 1974.

Seth, T. D., L. N. Agarawal, N. K. Satida, and M. Z. Hasan. The effect of lead and cadmium on liver, kidney and brain levels of cadmium, copper, lead, manganese, and zinc, and on erythrocyte ALA-D activity in mice. Bull. Environ. Contam. Toxicol. 16:190-196, 1976.

Shigematsu, I. et al. Discussion: Itai-Itai disease. Nippon Rinsho 33(6):2146-2164, 1975. (In Japanese).

Shimada, T., T. Watanabe, and A. Endo. Potential mutagenicity of cadmium in mammalian oocytes. Mutat. Res. 40:389-396, 1976.

Shiraishi, Y., and T. H. Yoshida. Chromosomal abnormalities in cultured leucocyte cells from Itai-Itai disease patients. Proc. Jpn. Acad. 48:248-251, 1972.

Shiraishi, Y., H. Kurahashi, and T. H. Yoshida. Chromosomal abnormalities in cultured human leukocytes induced by cadmium sulfide. Proc. Jpn. Acad. 48:133-137, 1972.

Shiroishi, K., T. Kjellström, K. Kubota, P. Ervin, M. Anayama, O. Vesterberg, T. Shimada, M. Piscator, T. Iuata, and H. Nishino. Urine analysis for detection of cadmium-induced renal changes with special reference to β_2-microglobulin. Environ. Res. 13:407-424, 1977.

Shiroishi, Y. Cytogenetic studies in 12 patients with Itai-Itai disease. Humagenetik 27:31-44, 1975.

Singerman, A. Clinical signs versus biochemical effects for toxic metals. In: Effects and Dose-Response Relationships of Toxic Metals. G. F. Nordberg (ed.). Elsevier, Amsterdam, 1976. p. 207-225.

Singh, K., and R. Nath. In vivo and in vitro effect of cadmium chloride on succinic dehydrogenase and lactate dehydrogenase activity on rat testes, plasma, and liver. Proc. Asia Oceania Cong. Endocrinol. 5th 1:204-211, 1975.

Singhal, R. L., Z. Merali, and P. D. Hrdina. Aspects of the biochemical toxicology of cadmium. Aspects of the biochemical toxicology of cadmium. Fed. Proc. Fed. Am. Soc. Exp. Biol. 35:75-80, 1976.

Sirover, M. A., and L. A. Loeb. Infidelity of DNA synthesis in vitro: Screening for potential metal mutagens or carcinogens. Science 194:1434-1436, 1976.

Skog, E., and J. E. Wahlberg. A comparative investigation of the percutaneous absorption of metal compounds in the guinea pig by means of the radio-isotopes--^{51}Cr, ^{58}Co, ^{65}Zn, ^{110}Ag, ^{115}Cd, ^{203}Hg. J. Invest. Dermatol. 43:187-192, 1964.

Smith, J. P., J. C. Smith, and A. J. McCall. Chronic poisoning from cadmium fume. J. Pathol. Bacteriol. 80:287-296, 1960.

Sonawane, B. R., M. Nordberg, G. F. Nordberg, and G. W. Lucier. Placental transfer of cadmium in rats: Influence of dose and gestational age. Environ. Health Persp. 12:97-102, 1975.

Sorenson, J. R. J., S. Sastry, and T. E. Kaher. Cadmium-induced hypertension in male Sprague-Dawley rats. Ann. Report of Center for Study of Human Environment, Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio, 1973. p. 93-96.

Sorsa, M., and S. Pfeifer. Effects of cadmium on development time and prepupal puffing patterns in D. melanogaster. Heriditas 75:273-277.

Spiegel, A. M., E. M. Brown, and G. D. Aurbach. Inhibition of adenylate cyclase by arsenite and cadmium: Evidence for a vicinal dithiol requirement. J. Cyclic Nucleotide Res. 2:393-404, 1976.

Squibb, K. S., R. J. Cousins, B. L. Silbon, and S. Levin. Liver and intestinal metallothionein: Function in acute cadmium toxicity. Exp. Mol. Path. 25:163-171, 1976.

Stancer, H., and T. Dardzonov. Zhivotnovud. Nauki 4:97-103, 1967.

Steltzner, M. F., D. A. Baron, and J. R. Esterly. Cadmium-induced lung injury. Lab. Invest. 32:457, 1975.

Stoll, R. E., J. F. White, T. S. Miya, and W. F. Bousquet. Effects of cadmium on nucleic adic and protein synthesis in rat liver. Toxicol. Appl. Pharmacol. 37:61-74, 1976.

Stowe, H. D. Biliary excretion of cadmium by rats: Effects of zinc, cadmium and selenium pretreatments. J. Toxicol. Environ. Health 2:45-53, 1976.

Strauss, R. H., K. C. Palmer, and J. A. Hayes. Acute lung injury induced by cadmium aerosol. Am. J. Pathol. 34:561-568, 1976.

Suda, T., N. Horiuchi, N. Otaki, S. Sesaki, and M. Kimura. Mechanisms of biological prevention against cadmium poisoning. J. Dent. Res. 53(Suppl. 5):1092, 1974.

Sugawara, C., and N. Sugawara. Cadmium toxicity for rat intestine, especially on the absorption of calcium and phosphorus. Nippon Eiseigaku Zasshi 28:511-516, 1974.

Sugawara, C., and N. Sugawara. The effects of cadmium on soluble proteins, enzymes, and essential metals of the duodenal mucosa. Arch. Environ. Contam. Toxicol. 6:121-128, 1977.

Sugawara, N. and C. Sugawara. Effect of cadmium, *in vivo* and *in vitro*, on intestinal brush border ALPase and ATPase. Bull. Environ. Contam. Toxicol. 14:653-656, 1975.

Sunderman, F. W., Jr. Metal carcinogenesis. *In*: Advances in Toxicology. Vol 2: Toxicology of Trace Elements. R. A. Goyer and M. A. Mehlman (eds.). Halstead Press, New York, 1977. p. 260-262.

Sutherland, D. J. B., B. K. Tsang, Z. Merali, and R. L. Singhal. Testicular and prostatic cyclic AMP metabolism following chronic cadmium treatment and subsequent withdrawal. Environ. Physiol. Biochem. 4:205-213, 1974.

Suter, K. E. Studies on the dominant-lethal and fertility effects of the heavy metal compounds methylmercuric hydroxide, mercuric chloride, and cadmium chloride in male and female mice. Mutat. Res. 30:365-374, 1975.

Suzuki, Y. Cadmium of metallothionein in liver and kidney after prolonged administration of cadmium. In: Proc. 47th General Assembly of Japan. Ind. Health Assoc. Nagowa. 1974. p. 124-125. Cited by Tanaka, K. Tox. Appl. Ph. 33:258 ('75) The 47th Annual Meeting of the Japanese Assoc. of Industrial Health, Nogoya, Japan, 1974.

Tada, N. Neuromuscular blocking action of cadmium and manganese in isolated frog striated muscles. Eur. J. Pharmacol. 40:67-75, 1976.

Tafanelli, R. F. Effects of intraperitoneal injections of cadmium chloride on gonads, liver and kidney of goldfish, Carassius auratus. Linn. Ph.D. Thesis, Oklahoma State University, Dept. of Zoology, Stillwater, Okalhoma, 1972.

Takahashi, T. Abnormal mitosis by some mutagens in Saccharomyces cerevisiae. Bull. Brew. Sci. 18:37-48, 1972.

Task Group on Lung Dynamics: Deposition and retention models for internal dosimetry of the human respiratory tract. Health Phys. 12:173-207, 1966.

Taylor, B. A., J. Heiniger, and H. Meier. Genetic analysis of resistance to cadmium-induced testicular damage. Proc. Soc. Exp. Biol. Med. 143:629-633, 1973.

Teare, F. W., P. Jasonsky, L. Renaud, and P. R. Pread. Acute effect of cadmium on hepatic drug-metabolizing enzymes in the rat. Toxicol. Appl. Pharmacol. 41:57-65, 1977.

Thind, G. S. Renal venous renin and systemic vascular reactivity in cadmium-hypertensive dogs. Clin. Res. 21:816, 1973.

Thind, G. S. Blood vessel wall characteristics in experimental hypertension. Angiology 25:752-763, 1974.

Thind, G. S., and G. M. Fischer. Cadmium and zinc distribution in cardiovascular and other tissues of normal and cadmium-treated dogs. Exp. Molec. Pathol. 22:326-334, 1975.

Thind, G. S., and G. M. Fischer. Plasma cadmium and zinc in human hypertension. Clin. Sci. Molec. Med. 51:483-486, 1976.

Thind, G. S., Biery, D. N., and Bovel, K. C. Production of arterial hypertension by cadmium in the dog. J. Lab. Clin. Med. 81:549-556, 1973.

Thind, G. S., K. F. Stephan, G. Karreman, and W. S. Blakemore. Vascular reactivity and mechanical properties of normal and cadmium-hypertensive rabbits. J. Lab. Clin. Med. 76:560-568, 1970.

Thung, P. J. Proteinuria in mice and its relevance to comparative gerontology. Expelle Alternsforsh. 4:195-198, 1956.

Troast, R. Cadmium: Position Document I. U.S. Environmental Protection Agency, Office of Special Pesticide Reviews, Cadmium Working Group, Washington, D.C., 1978.

Tsang, S., and A. Furst. *In vitro* inhibition of aryl hydrocarbon hydroxylase by heavy metals. Oncology 33:201-204, 1976.

Tsuchiya, K., and M. Sugita. A mathematical model for deriving the biological half-life of a chemical. Nord. Hyg. Tidskr. 53:105, 1971.

Tsuji, T., M. Nagata, Y. Ito, and H. Takigawa. Cadmium exposure in zinc refinery workers - Preliminary examination. Nippon Eiseigaku Zasshi 27:316-325, 1972.

U.S. Environmental Protection Agency Carcinogen Assessment Group's Assessment of Carcinogenic Risk from Population Exposure to Cadmium in the Ambient Air. External review draft. U.S. Environmental Protection Agency, Office of Research and Development, Washington, D.C. May, 1978.

Valberg, L. S., J. Haist, M. G. Cherian, L. Delaquerriere-Richardson, and R. A. Goyer. Cadmium-induced enteropathy: Comparative toxicity of cadmium chloride and cadmium-thionein. J. Toxicol. Environ. Health 2:963-975, 1977.

Vallee, B. L., and D. D. Ulmer. The biochemistry of cadmium, lead and mercury. Am. Rev. Biochem 41:91-128, 1972.

Voiner, A. C. The existence and role of cadmium in the organism of animals and man. Microelem. Zhizni Rast. Zhivotn. Tr. Konf. 1st 1950:580-583, 1952.

Vorob'eva, R. Investigation of the nervous system function in workers exposed to cadmium oxide. Zh. neuropat. psihait. 57:385-388, 1957.

Wahlberg, J. E. Percutaneous toxicity of metal compounds--A comparative investigation in guinea pigs. Arch. Environ. Health 11:201-204, 1965.

Washko, P. W., and R. J. Cousins. Metabolism of ^{109}Cd in rats fed normal and low-calcium diets. J. Toxicol. Environ. Health 1:1055-1066, 1976.

Washko, P. W., and R. J. Cousins. Role of dietary calcium and calcium binding protein in cadmium toxicity in rats. J. Nutr. 107:920-928, 1977.

Watanabe, H., H. Murayama, K. Ono, K. Araki, Y. Teraoka, H. Kosaka, and H. Takamatsu. Toxicity of cadmium dust inhaled by rats. Hyogóken Eisei Kenkyusho Kenkyo Hokoku 9:15-20, 1974a.

Waters, M. D., and D. E. Gardner. Metal toxicity for rabbit alveolar macrophages *in vitro*. Environ. Res. 9:32-47, 1975.

Webb, M. Protection by zinc against cadmium toxicity. Biochem. Pharmacol. 24:2767-2771, 1972.

Webb, M., and A. T. Etienne. Studies on the toxicity and metabolism of cadmium-thionein. Biochem. Pharmacol. 26:25-30, 1977.

Webb, M., and R. D. Verschoyle. An investigation of the role of metallothioneins in protection against the acute toxicity of the cadmium ion. Biochem. Pharmacol. 25:673-679, 1976.

Wills, J. H., R. LeFevre, B. K. Benitz, W. Dougherty, W. H. Talley, and F. Coulston. Chronic and multi-generation toxicity of cadmium for the rat and the Rhesus monkey. Environ. Qual. Saf. Supplement to Vol. 5, 1976.

Wolkowski, R. M. Differential cadmium-induced embryotoxicity in two inbred mouse strains. Toxicology 10:243-262, 1974.

World Health Organization Task Group on Environmental Health. Environmental Health Criteria for Cadmium. Summary. WHO, Geneva. 1977. 11 p.

Yau, E. T., and J. H. Mennear. Pancreatic metallothionein. Protection against cadmium-induced inhibition of insulin secretory activity Toxicol. Appl. Pharmacol. 39:515-520, 1977.

Yoshikawa, H., and K. Homma. Toxicity of inhaled metallic cadmium fumes in rats. Sangyo Igaku 16:212-215, 1974.

Zyka, V. Geochemical environment and incidence of cancer in Kutna Hora. Sb. Geol. Ved. Technol. Geochem. 11:155-181, 1973.

3. HUMAN EPIDEMIOLOGY

3.1 INTRODUCTION

Studies directly relating cadmium exposures to human health effects in various groups of the population are required to define the levels of exposure at which adverse health effects appear in order that the population segments at high risk can be identified. At present, except for some occupationally exposed workers and those dealing with population segments in the areas of Japan where Itai-Itai disease has been found, no such studies exist. Therefore, a logical chain from exposure to absorption level to adverse health effects for populations must be built. This can be done by (1) examining the distribution of cadmium sources to which humans are exposed, (2) assessing the levels of cadmium in blood or urine in the various population segments, and (3) correlating these findings with other research showing the adverse health effects of different levels of cadmium in human tissue within different population groups.

3.2 CADMIUM IN HUMAN POPULATIONS

The data for blood and urine cadmium levels in so-called "normal" populations presented here must be viewed with great caution for several reasons. The definition of "normal" varies enormously from study to study. Frequently, it is defined as "no known occupational exposure", but little evidence is presented to show how this was defined or established for the subjects. At times, the "normal" study group is drawn from patients who are believed to be free of disease since they require elective surgery, have had accidents, or are in other ways deemed to be free of metabolic or chronic disease. Finally, many of the population surveys were primarily designed

to study other pollutants, and the selection of the study population was stratified to represent gradients of the other pollutants in a single source such as air, lead paint, etc. Since cadmium in air does not always arise from the same sources as other pollutants, such stratification may in fact produce a biased rather than a random selection of the study population as far as cadmium is concerned.

Rapid changes in laboratory techniques also present a problem. Findings from earlier studies may not be comparable to those for more recent ones. In fact, many investigators comment that variations in the findings from different studies may be due primarily to variations in methodology. Sampling variations for the same individual must be added to this variance.

Variance within data for a single study should also be considered. It arises from so-called "within-group variance," which is due to differences among the subjects such as age, sex, exposure, etc. and also from biological differences in subjects within each of those same categories. Investigators, particularly the earlier ones, do not always provide information so that these sources of variance may be assessed.

3.2.1 Sources of Variations in Human Blood Cadmium Levels

A number of factors appear to affect human blood cadmium levels. Among the sources of variation discussed here in detail are demographic factors and geographic variation.

Quantitative measurements of cadmium at the levels encountered in biological media such as blood and urine are methodologically difficult, chiefly due to matrix effects. The extent of interference posed by the biological matrix will vary from method to method. At present the most common way to

assess cadmium levels in blood and urine is atomic absorption spectrometric analysis, a method with a number of problems.

Blood samples which are directly analyzed by atomic absorption spectrometry using the Delves Cup or the furnace technique may yield rather high cadmium values if care is not taken to adequately correct for smoke, or other, signal artifacts. Similar care must be exercised when anodic stripping voltammetry is employed, since the electrochemical behavior of the element is sensitive to the presence of ligating groups in the medium. Where feasible, it is probably most desirable to isolate cadmium from the matrix in which it occurs, using a solvent-extraction step.

An added problem is that of contamination of the blood or urine samples, particularly contamination of blood in collection tubes with cadmium-containing stoppers.

3.2.1.1 Demographic variability in human blood cadmium levels--Data relating age, sex, and race to human blood cadmium levels are very scarce. Only five studies reported values for children.

Ediger and Coleman (1973) recorded blood cadmium concentrations for 60 children. The major focus of the work reported was on the analytic methodology and no descriptions of these children were given. A median concentration of 0.05 μg/dl was reported.

Bogden *et al*. (1974) analyzed blood from 369 children being screened for lead poisoning in Newark, New Jersey. The children's ages ranged from 1 to 8 yr. Mean blood cadmium concentration was 0.3 μg/dl (no standard deviation given) with a range of 0.0 to 2.8 μg/dl. These children constitute a high-risk group for lead poisoning and are from inner-city ghetto sections

with old and dilapidated housing. Race was not reported, but it seems safe to assume that many were Black.

Smith et al. (1976b) examined blood cadmium levels for 26 hospitalized boys and girls aged 2 mo to 13 yr (mean age 4.9 yr). These were white middle- and upper-middle-class children from Salt Lake City, Utah, who had been hospitalized for elective surgery such as tonsillectomy. The mean value for blood cadmium levels was 0.66 ± 0.25 μg/100 gm with a range of 0.21 to 2.64 μg/100 gm.

Rosmanith et al. (1975, 1977) reported findings from a survey of 413 children from a north German industrialized town. The children, with an age range of 2 to 14 yr, were invited for examination according to a selection method based on their birthdate. The total population of 2 to 14 yr old children was estimated at 9,000; and 600 were selected to constitute the sample, with a response rate of 69 percent. The authors reported a mean blood cadmium level of 0.11 ± 0.23 μg/dl. Age and sex did not prove to be significant variables.

Delves et al. (1973) evaluated children with suspected lead poisoning and a control group hospitalized but without suspicion of lead intoxication and having no anemia, pica, mental retardation, or convulsions. These 89 control children were 4 days to 15 yr old, were both male and female, and had a mean blood cadmium value of 0.49 ± 1.5 μg/dl with range of 0.0 to 1.9 μg/dl. The lead-poisoning-suspected "case" group consisted of 189 boys and girls, aged 2 mo to 15 yr and with proportionately more children in the 3- to 6-year age category than controls. The mean value for "cases" was 0.57

μg/dl (no standard deviation given), and the range was from 0.0 to 7.9 μg/dl. The difference for the two exposure groups was not statistically significant. Differences by age and sex were also not significant.

In summary, there seems to be no age gradient among children's values for blood cadmium concentrations as, for example, has been found for blood lead concentrations where younger children show higher concentrations than older ones under the same exposure conditions. The explanation for the differences in the absolute values reported in the various publications is not apparent from the data reported. None of the mean values reported appear to differ much from many of those reported for "normal" adults, which will be discussed next.

When examining the blood cadmium concentrations reported for adults, it is important to note the recent custom of reporting separate values for smokers and nonsmokers. Invariably, regardless of the definitions utilized to categorize "smokers" and "non-smokers," the smokers have been found to have higher blood cadmium values. Further, it should be noted that most of the study populations are small and authors frequently neither report nor analyze the effect of age categories within their study groups. Equally frequently, sex differences are not reported when both sexes are represented in the study group.

Several reports have been omitted from the tabular presentation because of the problems encountered in interpreting their findings.

The largest normal population evaluated, the 1954 military recruits from a Chicago induction center, has been omitted from this table. Creason et al. (1976) found a mean value of 5.0, a median value of 3.6, and a range

of 1.0 to 30.0 μg/dl for these men aged 18 to 24. They speculate that this high value, which is not approached by any others reported for non-exposed populations, is probably due to contamination of blood samples from the containers used for storage since the materials were stored for about one and one-half years before analysis.

Also omitted from the table was the "19 cities" study. Kubota et al. (1968) selected 243 male residents from 19 cities in 16 states in the United States. Mean blood cadmium concentration was 1.77 μg/dl and the range was 0.5 to 14.6 μg/dl. The analytic technique used made it impossible to detect values under 0.5 μg/dl, and 111 subjects had such low values. This left 132 determinations. The authors stated that more than half of the determinations were $\leq$ 0.5 μg/dl and that the median was "about" 0.5 μg/dl.

Willden and Hyne (1974) reported on 19 male and 16 female controls who are described as "normal" adults. These investigators did not control for background in their procedure.

Table 3-1 shows the findings from the more recent studies which either evaluated "normal" adults or selected "normal" controls for some study or patient group. Concentrations grouped according to sex of subject are indicated, where possible, in Table 3-1. Generally there is good agreement among the concentrations reported within studies: males and females do not appear to show different concentrations within a given study. The studies which included both sexes but reported total means only also appear to be in the same range. Smokers show concentrations which are significantly higher in each study.

Table 3-1. "NORMAL" BLOOD CADMIUM LEVELS
(μg/dl)

Location	N(sex)	SS[a,b]	Age[a]	Mean ± SD[b]	Range	Procedure	Reference
Children							
U.S.							
Oklahoma City, OK	60(both)	--	12	Median = 0.05	--	Background corr.	Ediger and Coleman, 1973
Newark, NJ	369(both)	--	1-8	0.3	0.00-2.8	AA[d]: extraction hemolysates by APDC-MIBK procedure	Bogden *et al.*, 1974
Salt Lake City, Utah	26(both)	--	2 mo.-13 yr.; x = 4.9	0.66 ± 0.25	0.21-2.64	AA[d]: wet ashed samples extracted with Dithizone/ Chloroform	Smith *et al.*, 1976
Denver, CO	25(both) 25(both) 25(both)	-- -- --	1-4 5-9 10-19	0.12 ± 0.15[c]	< 0.04-1.77[c]	Flameless AA[d]: modified Delves cup procedure	Wysowski *et al.*, 1978
Germany							
Northern Industrial town	413(both)	--	2-14	0.11 ± 0.23	--	AA[d]: Delves cup procedure	Rosmanith *et al.*, 1977
England							
Urban	89(both)	--	4 days-15 yr.	0.49 ± 1.50	0-1.9	AA[d]: wet ashed sample	Delves *et al.*, 1973
Adults							
U.S.							
"working males"	153(M)	--	14->65	0.85; median = 0.70	0.34-5.35	Emission spectroscopy of wet ashed samples	Imbus *et al.*, 1963
S. Carolina workers in a lumber mill	40(M)	--	<39->60	0.42 ± .07	--	AA[d]: flame procedure on plasma	Hammer *et al.*, 1972

Table 3-1 (continued). "NORMAL" BLOOD CADMIUM LEVELS
(μg/dl)

Location	N(sex)	SS[a,b]	Age[a]	Mean ± SD[b]	Range	Procedure	Reference
Oklahoma City, OK	50(-)	--	Adults	0.06	0.02-0.2	Delves cup	Ediger and Coleman, 1973
Denver, CO	25(both)	--	20-39	0.12 ± 0.15[c]	<0.04-1.77[c]	Flameless AA[d]: modified Delves cup procedure	Wysowski *et al.*, 1978
	25(both)	--	≥40				
Houston, TX	41(M)	--	19-53	0.7 ± 0.85	--	AA[d]: with correction direct sample analysis	Johnson *et al.*, 1974; 1975
	27(M)	--	22-50	0.4 ± 0.44	--		
	36(F)	--	21-32	0.8 ± 1.70	--		
Belgium "workers"	33(M)	S	48±10	0.7 ± 0.6	--	Extraction	Lauwerys *et al.*, 1973
	11(M)	NS	31±14	0.7 ± 0.3	--		
	14(M)	S	30±7	1.2 ± 1.5	--		
	15(M)	NS	28±9	0.8 ± 1.8	--		
"workers"	22(M)	S	51±2	0.70 ± 0.10	--	Extraction	Lauwerys *et al.*, 1974
"workers"	110(M)	--	Adults	0.58 ± 0.21	--	Extraction	Roels *et al.*, 1974
Germany village	66(both)	S	Adults	0.33 ± 0.19	0.10->0.8	AA[d]: Delves cup procedure	Einbrodt *et al.*, 1976
village	103(both)	NS	Adults	0.22 ± 0.08	<0.1-0.49		
West Germany --	37(both)	--	Adults	0.95	0.4-1.9	Flameless AA[d] of hemolysates	Stoeppler *et al.*, 1974

Table 3-1 (continued). "NORMAL" BLOOD CADMIUM LEVELS (μg/dl)

Location	N(sex)	SS[a,b]	Age[a]	Mean ± SD[b]	Range	Procedure	Reference
Sweden							
--	25(M)	S	20-55	0.23	0.06-0.61	Background corr.	Ulander and Axelson, 1974
--	19(M)	NS	20-55	0.06	0.03-0.12		
--	20(F)	S	20-55	0.20	0.05-0.76		
--	25(F)	NS	20-55	0.05	0.02-0.10		
Denmark							
--	110(both)	--	0-80	1.26	0.5-4.5	Graphite atomizer	Nygaard, 1974
--	31(M)	--	21-71	1.64 ± 0.85	0.3-4.8	Flameless AA[d]	Clausen and Rastogi, 1977a; 1977b
	23(F)	--	21-73	(combined)	(comb.)		
Scotland							
Renfrew	34(F)	--	58.6±6.4	0.27 ± 0.19	--	AA[d]: APDC-MIBK extraction of hemolysates	Beevers *et al.*, 1976a
	36(M)	--	58.6±6.3	0.20 ± 0.13	--		
	35(both)	S	45-64	0.32 ± 0.16	--		
	35(both)	NS	All	0.18 ± 0.08	--		
Holland							
Arnheim	84(F)	NS	20-50	$\bar{X}g$ = 0.04	0.02-0.25	Flameless AA[d]	Zielhuis *et al.*, 1977
	61(F)	LS	20-50	$\bar{X}g$ = 0.06	0.2-0.24		
	77(F)	HS	20-50	$\bar{X}g$ = 0.07 (0.2 calculated as 0.1)	0.02-0.44		

[a]Information not published is indicated by --.

[b]SS: smoking status; S: smokers; NS: non-smokers; LS: light smokers; HS: heavy smokers.
SD: standard deviation. Arithmetic means are given unless indicated by $\bar{X}g$ to note geometric mean.

[c]Determined for all groups combined

[d]AA: atomic absorption

It is difficult to interpret the differences among various study findings; most likely they are due to variation in methods of analysis. There are not enough studies from any one country, except perhaps the United States, to consider the question of differences among countries. It is quite possible that smoking habits vary among different countries for males and females and for urban and rural populations.

Some additional studies investigated members of "normal" population segments selected for study of cadmium or combinations of cadmium and other heavy metals.

Imbus et al. (1963) studied chromium, boron, and nickel as well as cadmium in the blood of 154 volunteers. These consisted of 100 workers selected from among Cincinnati, Ohio, employees of 15 companies and nearby farms. An additional 54 men were selected from metropolitan New York, Denver, Miami, and Portland, Oregon. Altogether, 18 types of industries were represented. The distribution of age and occupational categories approximately corresponds to the U.S. male working population. The median for blood cadmium concentration was 0.70 μg/100 g, the mean 0.85, and the range 0.34 to 5.35 with the 95th percentile at 1.68 μg/100 g.

Hammer et al. (1972) evaluated workers with three levels of occupational exposure to cadmium. These were all Black males from South Carolina. The low-exposure group worked in a lumber mill, while exposed groups worked either continuously or intermittently exposed to cadmium in a plant producing superphosphate fertilizer. Mean blood cadmium concentration for the 40 low-exposure group subjects was 0.42 ± 0.7 μg/dl, lower than that for the two higher exposure groups.

Ediger and Coleman (1973), as mentioned above, reported concentrations found in the course of a methodological study. They report a mean concentration of cadmium of 0.06 μg/dl for 50 adults.

The "Houston Study" conducted by Johnson et al. (1975) reported concentrations for controls selected for three groups with risk of exposure to air pollution by working in traffic, in parking garages, or by living near a freeway. The means reported represent four blood samples per individual collected over time, and there was variance between tests for some groups. Controls for traffic policemen (N = 41) aged 19 to 53 yr had a mean concentration of 0.8 ± 0.85 μg/dl, controls for garage attendants (N = 27) aged 22 to 50 yr had a mean of 0.4 ± 0.44 μg/dl, and controls for women living near a freeway (N = 36) aged 21 to 32 yr had a mean of 0.8 ± 1.7 μg/dl.

Three studies from Belgian investigators are in the literature. Lauwerys et al. (1973) reported on exposed and nonexposed factory workers by sex and smoking status. The mean blood cadmium concentration for the nonexposed smokers and nonsmokers by sex are shown in the table. A later report by this group (Lauwerys et al., 1974) showed that 22 male workers selected as nonexposed controls had a mean concentration of 0.7 ± 0.1 μg/dl. Roels et al. (1974) reported on concentrations for 110 male workers selected as controls. Mean blood cadmium concentration was found to be 0.58 ± 0.21 μg/dl.

Einbrodt et al. (1976) evaluated blood for all 169 adults living in a small North German village known to be without environmental cadmium sources. The findings were presented for smokers and nonsmokers without definition

of age at adulthood or further definition of smoking status. Means of blood cadmium concentrations found were 0.22 ± 0.08 μg/dl for nonsmokers, while smokers showed a mean of 0.33 ± 0.19 μg/dl which is a statistically significant difference. Stoeppler et al. (1974) reported a mean of 0.95 μg/dl for 37 adults, with a range from 0.4 to 1.9 μg/dl.

Ulander and Axelson (1974) reported concentration means for smokers and nonsmokers. The differences between smokers and nonsmokers were statistically significant as was the difference between younger and older male smokers.

Nygaard et al. (1974), using a graphite atomizer procedure, found a mean blood cadmium level of 1.26 μg/dl (range 0.4 to 4.5 μg/dl) in a Danish population of 110 males and females ranging in age from newborn to 80 years old. Clausen and Rastogi (1977a,b) reported on 54 Danish adults. They found a mean blood cadmium of 1.64 ± 0.85 μg/dl with a range from 0.3 to 4.8 μg/dl.

Beevers et al. (1976a) reported concentrations for individuals found to be normotensive in a hypertension screening clinic. They were matched by age and sex to hypertensives selected for a study of any association between hypertension and cadmium concentrations. The difference between concentrations for smokers and nonsmokers was significant, but, for hyper- and normotensives, no significant difference was found.

Zielhuis et al. (1977) evaluated the blood cadmium concentrations of 222 housewives from Arnheim, the Netherlands, who were married to blue-collar or lower-income, white-collar workers. All were volunteers, and their smoking status was ascertained. The concentrations and geometric

means were the following: 84 non-smokers, 0.04 μg/dl with a range of < 0.02 to 0.25 μg/dl; 61 light smokers (1 to 9 cigarettes/day), 0.06 μg/dl with a range of < 0.02 59 0.24 μg/dl; 77 heavy smokers (≥ 10 cigarettes/day), 0.07 μg/dl with a range of 0.02 to 0.44 μg/dl. (The values < 0.02 were calculated as 0.01 μg/dl.) Non-smokers differed significantly from light and heavy smokers.

Wysowski et al. (1978) studied cadmium exposure in a community near a smelter (Denver, Colorado). Whole blood and urine specimens were obtained from 250 individuals living within 2 km of the smelter, as well as from a control population of 105 residents. Whole blood values, obtained by flameless atomic absorption methods, showed median blood levels of the "smelter" and "control" groups of 0.05 and 0.07 μg/dl, respectively. No statistical significant differences were obtained in the study, except between smokers and non-smokers; that is, smokers had higher blood cadmium values than non-smokers.

The Japanese research has not yielded blood cadmium data. Presumably the utilization of urine cadmium as an indicator is due to the usefulness of urine analyses in determining proteinuria.

3.2.1.2 Other variation--Only one study (Hecker et al., 1974) compared "acculturated" and "unacculturated" groups: adult volunteer blood donors in Ann Arbor, Michigan, and Yanomamo Indians from the interior of Venezuela. Blood cadmium determinations were done for 47 of the 100 people from Ann Arbor and 90 of the 137 Indians. The values for the Indians were a mean of 1.43 ± 1.19 μg/dl whole blood with a range of 0.3 to 5.7 μg/dl. The Ann Arbor group had a mean of 1.71 ± 1.89 μg/dl and a range of < 0.1 to 9.6

μg/dl. The values are high and probably attributable to the analytic methodology. Clearly these are not enough data to assess blood cadmium levels for populations in remote areas with little or no technological advance.

Urban and rural differences also cannot be evaluated at this time. There are no studies reporting blood cadmium levels for rural populations.

3.2.1.3 Occupational exposure and blood cadmium--The extensive literature dealing with the effects of high cadmium exposure levels at places of work will not be reviewed here. The cadmium in dust and fumes is inhaled, and exposed personnel have consistently shown levels of blood cadmium concentrations that have been considered abnormal. Presumably, faulty hygiene will contribute to additional exposure by transfer of dust from hands and clothing to food. Piscator *et al*. (1976) showed that cigarettes and tobacco handled at work by workers who were exposed to cadmium oxide dust have a higher cadmium content than these smoking materials ordinarily show.

There have been no studies exploring the effect of workers carrying cadmium dust home and contributing to the exposure of other family members, although this possible route of secondary exposure should be assessed in view of recent reports of lead exposure by this route.

3.2.2 Sources of Variation in Human Urine Cadmium Levels

As noted before in the discussion of the determination of blood cadmium values, cadmium measurement in biological media can be fraught with analytical errors. Urine is a particularly vexing medium for trace metal analysis, because of both the high content of inorganic salts and the presence of organic substances. In particular, the atomic absorption

analysis of cadmium in urine is complicated by both smoke artifacts and the levels of chloride ion present. Solvent extraction of ashed samples should be carried out where possible.

Studies of the normal population, control, or reference cases cited before also frequently determined concentrations of cadmium in urine. Table 3-2 shows the concentrations found in those studies, as well as those reported by Ross and Gonzalez (1974), Kubasik and Volosin (1973), Tada et al., (1972), Fukabori and Nakaaki (1974), and Miller et al., (1976). The excretion rate for cadmium by urine in normal persons is age dependent. There is an increase until the late fifties, followed by a decline. The mean urine cadmium concentrations reported for the studies listed in Table 3-2 indicate a general daily urine cadmium excretion level between 1 and 2 μg day. The results of the studies listed in the table, however, obscure the effect of age.

In contrast, two other recent studies provide information on age relationships. Tsuchiya et al. (1976) reported on a study of 609 Tokyo residents which permits analysis of the urine cadmium concentrations by age intervals. Figure 3-1 shows the distribution of mean urine cadmium concentrations by age as well as the standard deviations. The authors also collected data on concentrations of cadmium in the renal cortex, renal medulla, liver, pancreas, heart muscle, and aorta. They examined 169 cadavers of residents of Tokyo with no known disease or poisoning, who had died of accidental causes of death. The analysis of tissue concentrations permitted a calculation of total body burden of cadmium by age. The authors found the mean urine cadmium concentration for ages 30 to 59 yr to be 1.7 ± 1.5 μg/l, with an upper-range value of "about 10 μg/l."

Table 3-2. "NORMAL" URINE CADMIUM LEVELS[a]

Location	N(sex)	Age	Mean ± SD	Range	Unit	Procedure	Reference
Children							
German Industrial town	413(both)	2-14	0.50 ± 0.40	--	μg/l	AAS	Rosmanith et al., 1977
Adults							
U.S.							
Cincinnati, Ohio & 4 other met. areas	154(M)	14->65	1.59 ± 4.13 median = 1.15	<0.5-10.8	μg/l	Cholak and Hubbard method	Imbus et al., 1963
S. Carolina	40(both)	<39-60+	1.04	--	μg/l	AAS Parker-Elner	Hammer et al., 1972
--	13(--)	--	2.9	0-10.1	μg/day	Extraction carbon rod atomizer	Kubasik and Volosin, 1973
--	20(--)	--	1.5 ± 0.7	0.4-3.7	μg/l	Graphite atomizer	Ross and Gonzalez, 1974
Houston, TX	27(M) 36(M)	22-50 21-32	0.5 0.6	-- --	μg/l	Acidified urine and Delves cup procedure	Johnson et al., 1974
Houston	41(M)	19-53	0.6 ± 0.44	--	μg/l	Acidified urine and Delves cup procedure	Johnson et al., 1975
Japan							
--	81(--)	20-60	1.39	0.25-4.0	μg/l	Extraction	Tada et al., 1972
--	5(--)	27-37	2.56	1.7-3.7	μg/day	Extraction	Taguchi et al., 1972
--	374(--)	20-60	$\bar{X}$g's = 0.64 + 0.65 -0.33	0.05-3.68	μg/l[e]	--	Fukabori and Nakaaki, 1974
			1.06 ± 1.06 -0.33	0.24-6.72	μg/24 hr	--	

Table 3-2 (continued). "NORMAL" URINE CADMIUM LEVELS[a]

Location	N(sex)	Age	Mean ± SD	Range	Unit	Procedure	Reference
Belgium							
--	33(M)[c]	48±2	2.0 ± 0.2	--	μg/g creatinine	Extraction	Lauwerys *et al.*, 1973
	11(M)[d]	33±4	1.0 ± 0.2	--			
	14(F)[c]	30±2	2.6 ± 0.8	--			
	15(F)[d]	28±2	1.5 ± 0.5	--			
--	110(M)	--	1.79 ± 1.68	--	--	Extraction	Roels *et al.*, 1974
Australia Brisbane	22(both)	Adults	1.1	< 0.5-2.5	μg/l	AAS: APDC-MIBK flameless	Miller *et al.*, 1976

[a]Arithmetic mean unless otherwise indicated; geometric mean: $\bar{X}$g.; information not reported: --.

[b]AAS: atomic absorption spectroscopy.

[c]Smokers.

[d]Non-smokers.

[e]Adjusted individually for specific gravity.

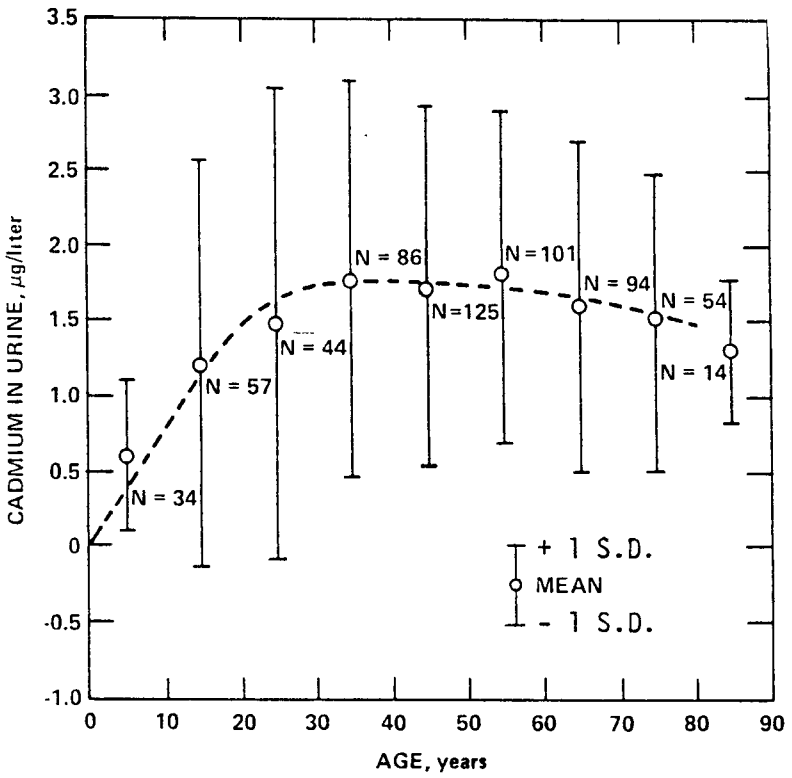


Figure 3-1. Distribution of mean urine cadmium concentrations by age. (From Tsuchiya et al., 1976.)

It was pointed out that it is essential that as many cases as possible--more than 20 or 30--within the same sex and age categories be analyzed in order to meet the problem of large individual variation. Johnson et al. (1977) reported urine cadmium concentrations for 86 males in Dallas, Texas, included as part of the collaborative study undertaken in Japan, Sweden, and the United States. Table 3-3 shows their findings. Age-related changes were found in the data with an increase occurring until 40 to 49 yrs and then a subsequent decrease. In another study, by Elinder et al. (1978), cadmium concentration in the urine of 131 Swedes, including 50 pairs of identical twins, were measured. As seen in other studies, urinary cadmium increased with age and was higher among smokers than among non-smokers. The daily cadmium output among non-smokers in various age

groups corresponded better with total kidney burden than with daily dietary intake.

In the recent report of Tati et al. (1976), involving unexposed Japanese subjects, the age/cadmium-excretion relationship was established using males and females up to 75 yr of age. The distribution of urinary cadmium levels followed essentially a log-normal pattern, with levels increasing with age up to the 60- to 69 yr age group in males and the 50- to 59-year-age group in females. This reflects an increasing body burden with age (Friberg et al., 1974), due to the relatively long half-life of cadmium in major organs which is estimated at 17 to 38 years.

Table 3-3. URINE CADMIUM LEVELS FOR "NORMAL" MALES IN DALLAS, TEXAS, DETERMINED BY ATOMIC ABSORPTION[a,b] (μg/l)

Age (years)	N	Geometric mean	Confidence interval
0-9	15	0.415	0.289-0.553
10-19	8	0.334	0.174-0.516
20-29	16	0.422	0.300-0.556
30-39	7	0.496	0.305-0.716
40-49	16	0.797	0.642-0.966
50+	24	0.704	0.582-0.835

[a]From Johnson et al., 1977

[b]5th to 95th percentile range: 0.148 to 1.293

The report of Wysowski et al. (1978), mentioned earlier under Section 3.2.1, on blood cadmium levels in residents living near a smelter also included urine cadmium values of 0.9 μg/l and 0.8 μg/l, respectively, for residents close to a smelter and a control group. No significant differences were found, except for smokers having significantly higher urine cadmium levels than non-smokers.

The literature relating occupational exposure to variations in urine cadmium concentrations will not be reviewed here except to note that it has been suggested that these concentrations may increase when renal tubular damage exists, as indexed by proteinuria and glycosuria. This increase is independent of age. Further, little data exist which relate variations in urine cadmium concentrations to food and water levels of the metal, except for Japanese populations; and these are discussed later in relation to Itai-Itai disease.

3.2.3 Sources of Cadmium Variation in Human Hair

Concentrations of cadmium in hair has been evaluated as an indicator of exposure to the metal. Several studies have been reported where hair cadmium levels have been correlated with environmental exposures. Hammer et al. (1971) analyzed hair samples from fourth-grade boys from five cities rated as varying in overall environmental cadmium levels. The analysis showed that arithmetic and geometric means varied by city in accordance with the city's exposures rating. The geometric means ranged from 2.1 to 0.7 parts per million (ppm).

Pinkerton et al. (1974) analyzed hair samples from three communities which varied in their levels of environmental cadmium. Geometric means of

hair cadmium concentrations, while different for each community, did not follow the exposure gradient.

Creason et al. (1975) reported significant correlations between cadmium content of hair and exposure as measured by content in dustfall and housedust in metropolitan New York. The exposure measurements came from the CHESS network, and the three communities showed a gradient for cadmium exposure. A total of 498 participants provided hair samples and sociodemographic information. The geometric mean hair cadmium concentrations in children aged 0 to 15 yr were 0.88 ± 0.42 to 1.85 μg/g. For adults, the values were 0.76 ± 0.33 to 1.74 μg/g. No significant association with exposures were found, however, although other trace metals also evaluated did show such association.

Hambidge et al. (1974) reported on hair trace-metal levels for 18 young adults from Denver, Colorado; 11 from Chandigash, India; and 25 from Bangkok, Thailand. The analytic method for assessing cadmium concentrations gave a detection level of 0.1 ppm; and 48 percent of Denver, 12 percent of Chandigash, and 72 percent of Bagkok samples could be detected. In view of this problem the results for cadmium do not appear to be very meaningful.

McKenzie and Neallie (1974) reported on hair cadmium values but concluded that hair cadmium levels are not useful in populations with low exposure, since no significant differences were found among the various study populations.

Rosmanith et al. (1975, 1977) reported no significant findings for hair cadmium levels in their study of 413 children in a northern German industrial town.

In summary, assessment of cadmium levels in hair appears to be of questionable utility, unless used jointly with urine and blood cadmium determinations. Technical problems in collecting appropriate hair samples and in analytic techniques require further study. Also, the process of cadmium deposition in hair is not well understood.

3.3 RESULTS OF AUTOPSY STUDIES

Crucial to assessment of the effects of cadmium on human populations is the necessity of determining key organ levels of the metal and, where possible, total body burden. Generally it is not feasible to assess these levels in humans other than through autopsy studies, and a number of investigators have carried out such surveys of selected organ levels. These studies can be roughly classed into case studies concerned with specific diseases or population studies as discussed below. Before proceeding, it should be noted that some workers (Harvey *et al.*, 1975) have recently carried out *in vivo* neutron activation analysis studies of cadmium levels in organs of human volunteers. Such an approach, however, is still considered to be largely experimental and is typically not feasible as a method for studying large populations.

It is necessary to point out some limitations of the data obtained from autopsy studies. The cases coming to autopsy do not really constitute a representative sample of a given population. The requirements for performing an autopsy vary from country to country, and different population segments differ significantly in their willingness to consent to autopsies not legally required. It is also well known that this attitude is related to social status, occupation, and housing, all of which are factors associated with different degrees of exposures to various toxins and

pollutants and with nutritional and health status. The technical problems of speed, collection of information retrospectively, and the proportion of dead without living contacts all add to the difficulty of obtaining reliable data needed to analyze and interpret findings. Finally, there is the problem of defining "normal" or "healthy" individuals. Usually, accidental deaths are defined as "normal" or "healthy," and the quality of the examination of accident cases to determine this status may also vary.

Autopsy studies which report findings for unselected population groups and which are large enough to present cadmium concentrations further categorized by age give support to the findings from the earlier studies which show that cadmium concentrations in liver increase with age but may taper off after 60 or 70 years of age. Concentrations in the kidney also increase with age until about age 50 is reached; then there is a decrease. Elinder et al. (1976) reported on 292 autopsies from Stockholm. The age distribution for the 292 cases is shown in Table 3-4. This table also presents geometric means ($\bar{X}$) and standard deviations (SD). Figure 3-2 presents the findings for kidney cortex concentrations.

Tsuchiya et al. (1976) reported on 106 autopsies for Tokyo residents dying of accidental causes. Table 3-5 presents the findings for renal cortex cadmium concentrations. The age-related pattern of change is clearly evident.

Miller et al. (1976) in Australia found renal cadmium concentrations that followed the same age-associated pattern in 91 autopsies. Figure 3-3 presents their findings for means of concentrations for kidneys.

Table 3-4. CADMIUM IN HUMAN LIVER[a,b]
(μg/g wet weight)

		Age (yr)									
		0 - 9	10 - 19	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70 - 79	80 - 89	90 - 99
All subjects:	N	7	24	33	34	40	43	39	41	25	6
	$\bar{X}$	0.26	0.51	0.60	0.60	0.68	0.85	1.02	1.05	0.53	0.83
	SD	1.66	1.88	1.88	2.48	2.04	2.24	2.25	2.77	2.80	1.81
Males:	N	5	18	19	22	24	21	19	20	14	3
	$\bar{X}$	0.33	0.55	0.58	0.51	0.62	0.77	0.84	0.96	0.59	0.53
	SD	1.54	1.82	1.98	2.80	2.01	2.56	2.26	2.91	2.21	1.23
Females:	N	2	6	14	12	16	22	20	21	11	3
	$\bar{X}$	0.15	0.40	0.63	0.80	0.79	0.94	1.22	1.14	0.46	1.29
	SD	1.05	2.06	1.76	1.76	2.07	1.95	2.18	2.69	3.67	1.65
Nonsmokers:	N	...	...	6	1	1	6	11	14	12	2
	$\bar{X}$	...	...	0.52	1.01	0.66	0.48	0.72	0.94	0.46	0.72
	SD	...	...	1.77	...	...	2.07	2.78	3.13	3.26	2.16
Smokers:	N	...	...	7	10	13	15	15	13	1	1
	$\bar{X}$	...	...	0.77	0.57	0.77	1.14	1.24	1.32	0.89	2.17
	SD	...	...	1.55	2.63	2.01	2.72	2.14	2.58	...	...

[a]Mean ($\bar{X}$) and standard deviation (SD) are geometric. Tolerance intervals are calculated by multiplying or dividing $\bar{X}$ by SD.

[b]From Elinder et al., 1976.

Gross et al. (1976) reported on a series of 106 autopsies, from Cincinnati, Ohio, and Table 3-6 shows the arithmetic mean ($\bar{X}$) and standard deviations (±SD) for age categories. The concentrations for liver increased until the sixth decade, when they appeared to level off. Cadmium concentrations for kidney increased until ages 45 to 54 and then showed a decrease.

Table 3-5. CADMIUM CONCENTRATION IN HUMAN RENAL CORTEX BY AGE: MEANS AND 99% LEVEL OF SIGNIFICANCE[a] (μg/g)

Age	Mean	S.D.	99% Level of significance[b]	N
0 ~ 9	4.75	5.07	17.43	13
10 ~ 19	33.2	31.48	--	5
20 ~ 29	46.26	21.53	100.09	38
30 ~ 39	69.21	29.31	142.49	27
40 ~ 49	85.07	47.49	203.8	11
50 ~ 59	125.3	56.74	--	6
60 ~ 69	125.88	14.20	--	3
70 ~ 79	37.9	--	--	1
80 ~	94.68	18.7	--	2
Total	57.99	41.85	162.62	106

[a]From Tsuchiya et al., 1976.

[b]$\bar{X}$ + (S.D. x 2.5)

Table 3-6. AGE GROUP MEANS AND STANDARD DEVIATIONS FOR TISSUE CADMIUM[a] (ppm wet weight)

	Liver			Kidney		
Age group	N	$\bar{X}$[b]	±SD	N	$\bar{X}$	±SD[c]
Abortuses	19	0.01	0.00	19	0.07	0.06
0-1 mo	7	0.01	0.01	7	0.05	0.04
1-23 mo	9	0.05	0.05	9	0.13	0.09
2-5 yr	7	0.33	0.35	7	13.33	22.72
6-12 yr	4	0.66	0.49	4	6.23	6.71
13-18 yr	11	0.97	0.69	11	8.57	3.97
19-24 yr	10	0.82	0.54	10	13.73	6.99
25-34 yr	10	1.25	0.75	10	24.40	14.10
35-44 yr	6	0.88	0.66	6	29.62	14.97
45-54 yr	3	1.75	1.86	2	39.35	13.79
55-64 yr	9	1.96	1.30	9	30.09	17.22
65+ yr	10	1.97	1.08	10	20.89	12.26
Total	106	0.88	1.19	105	13.65	17.60

[a]Adapted from Gross et al. (1976).
[b]Arithmetic mean.
[c]Standard deviation.

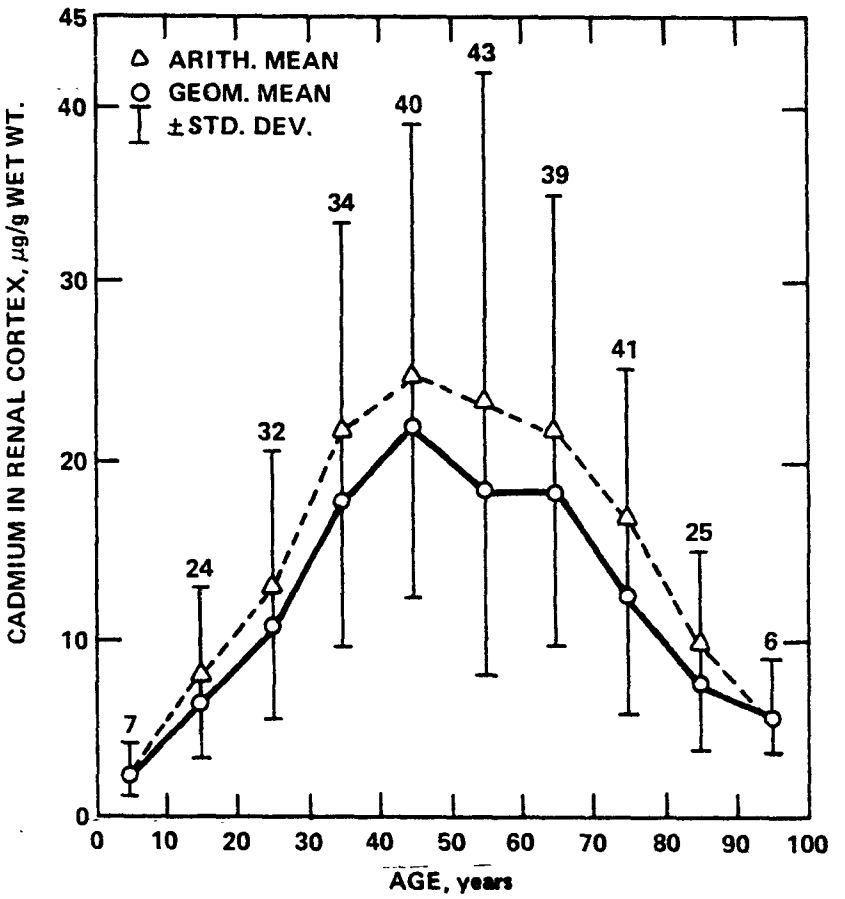


Figure 3-2. Geometric and arithmetic means of cadmium concentration in kidney cortex are shown for each decade of life. (From Elinder et al., 1976.)

Syverson et al. (1976) in Bergen, Norway, examined liver and kidney cadmium concentrations in 76 autopsies. These authors also found the age-associated patterns for cadmium concentrations in liver and kidney. They reported data for urban and rural residence, and Table 3-7 presents these findings. Smoking status also showed higher values for cigarette smokers than for non-smokers, and blue-collar workers had higher concentrations than white-collar workers and "others," a group consisting mostly of housewives.

A further group of reports for autopsy studies did not present data for general populations with a wide distribution by age. The persons reported on either constituted a single age group or were selected to investigate the association of cadmium and specific diseases. Data concerned with "normal," "reference," or "control" groups has been selected from such studies for presentation.

Morgan (1970) in Birmingham, Alabama, studied cadmium concentrations for older males. The "normal" group's mean age was 61 years and included 55 persons. The mean and standard deviation for liver cadmium concentration was 182 ± 99 μg/g ash and 2406 ± 1299 μg/g ash for kidney cadmium concentrations.

Ostergaard et al. (1977b) presented data for 61 cases where cigarette smoking status was known. Non-smokers (N = 19) showed the following for whole kidney μg/g ash: Arithmetic mean (and range): 1106 (347 to 2466) μg/g ash, and a geometric mean of 953. The 42 smokers showed the following: for those with less than 20 cigarettes per day (N = 11), arithmetic mean (and range): 2415 (947 to 3821) μg/g ash and geometric mean of 2242 μg/g ash; for heavy smokers (N = 12) using 20 or more cigarettes per day:

Table 3-7. MEAN CADMIUM VALUES RELATED TO PLACE OF RESIDENCE[a]

Residence	N	Age (year) Geometric Mean	Liver Cd (μg/g dry weight) Mean	SD	Renal cortex Cd (μg/g dry weight) Mean	SD	Renal medulla Cd (μg/g dry weight) Mean	SD
Urban	52	65.9	8.1	± 5	101	± 60	62	± 42
Rural	24	51.0	8.1	± 5	98	± 50	54	± 30
Total	76	60.8	8.1	(1.1-24.3)[b]	100	(22-297)[b]	57	(6.7-171)[b]

[a]Adapted from Syversen *et al*. (1976).

[b]Range.

arithmetic mean (and range); 2778 (961 to 7493) μg/g ash and geometric mean of 2310 μg/g ash.

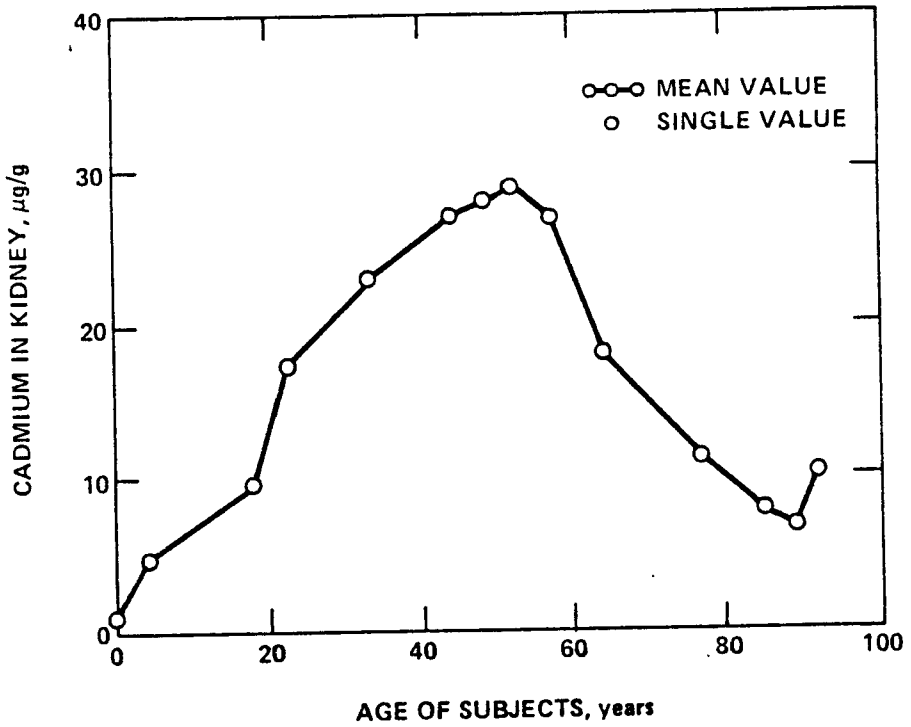


Figure 3-3. Cadmium in whole kidney tissues and its relationship to age. (From Miller et al., 1976.)

Lewis et al. (1972) in Boston, Massachusetts, examined liver and kidney tissue from 172 cadavers. The 161 males had a mean age of 61 ± 1.0 yr, and the mean age of the 11 females was 70 ± 3.1 yr. Total mean cadmium content for kidney (N = 171) was 9106 ± 0.50 mg and that for liver (N = 172) was 2.92 ± 0.14 mg. When these findings were examined for the effect of smoking, differences for smokers and non-smokers were found as follows: Non-smokers (N = 34) had a mean of 4.16 ± 0.51 mg for kidney, smokers (N = 138) 10.28 ± 0.57 mg. Means for liver were: non-smokers 2.28 ± 0.25 mg, smokers 3.06 ± 0.16 mg.

Kidney cadmium levels for non-smokers and smokers were measured by Johnson et al. (1977). Cadmium levels were significantly greater ($p < 0.001$) for smokers, the difference between the two groups being 6.9 μg/g average concentration.

3.4 EPIDEMIOLOGICAL STUDIES OF CADMIUM EXPOSURE IN JAPAN

A number of comments appear in the preceding Health Effects sections dealing with the pathophysiological features of cadmium as they have been unveiled over the last two decades in cadmium-polluted areas of Japan, with emphasis on the most serious aspect of population response, Itai-Itai or "Ouch-Ouch" disease. A considerable effort has also been documented in connection with other areas of cadmium pollution in Japan other than the Jintsu River basin, or Itai-Itai belt, and the epidemiological data will be considered in two sections: Itai-Itai disease and other studies of cadmium pollution in Japan.

Some general comments are in order with reference to the nature of the Japanese epidemiological studies which have been carried out so far.

(1) Different investigators have employed various techniques to assess the indicators of adverse health effects in these population groups under study. Until recently, when attempts were made in Japan to standardize the way in which one assesses cadmium-associated proteinuria, which is the most common indicator of chronic cadmium exposure, the methods for increased protein excretion were rather crude, semi-quantitative, and nonspecific. Thus, it is not always possible to compare these types of data gathered by different investigators; Friberg et al. (1974) discuss this difficulty in some detail.

(2) Questions arise in a number of cases as to the appropriateness of the control population groups taken for study with particular reference to close matching for age, diet, and nutritional status. For example, it is not apparent that some controlling for dietary cadmium intake constitutes true non-polluted diet groups.

(3) Given the retrospective nature of many of the studies, difficulty arises in attempting to draw correlations between factors such as diet and the present health status of the various exposure groups. For example, the exposure in many cases has occurred over a number of years, several decades in some instances, while assessment of dietary cadmium is based on data collected much later, after the onset of overt effects. Ideally, one would like to have had a time-concordant profile of changes in dietary cadmium, if any, over this period.

(4) One can argue that Japan constitutes a unique cadmium-exposure situation owing to heavy population density, the very close proximity of industrial to agricultural and other human activities, the geochemical nature of the ores mined and processed as to cadmium content, etc.; so its experience with cadmium may, therefore, not be applicable to the United States. As noted earlier, however, the collective Japanese experience with cadmium constitutes a classic case of pollution in a heavily industrialized society which persisted for a number of years with little telling effect and in ways which remained unidentified and unsuccessfully treated.

3.4.1 Itai-Itai Disease

The chronology of the development of Itai-Itai disease and the studies directed thereto have been extensively considered elsewhere (Friberg et al., 1974; Fulkerson and Goeller, 1973), and the earlier literature evaluation will not be repeated here, but some of the more recent data will be considered.

In Friberg et al. (1974) a good case was made for the etiological role of cadmium in the development of Itai-Itai disease, tubular proteinuria

with osteomalacia, and severe osteoporosis afflicting older females ($\leq$ 40 yrs) in the Fuchu area of Toyama Prefecture. As noted elsewhere in this report, the victims also had histories of marked nutritional deficiencies.

In Cadmium in the Environment III (Friberg et al., 1975), some more recent studies from the Itai-Itai region were discussed.

Shiroishi and Yoshida (1972) selected a group of 123 men and 119 women over 40 years of age in S-village in the Fuchu area as an exposure group and used as a control group 75 men and 86 women in a different area. In their study, the prevalence of proteinuria increased from about 10 percent in the 40- to 50-year-age group to about 50 percent in the 70- to 80-year-age group. Proteinuria was assessed using the Kingsbury-Clark method as well as disc electrophoresis, while test-tape and OTB methods were employed for glucosuria.

In the study of Fukuyama et al. (1972), the time of residence in the Fuchu area was correlated with cadmium excretion and renal dysfunction. Cadmium excretion was seen to reach a maximum at 40 years of living in the area, and after 45 years, almost all of the individuals showed renal dysfunction.

In the dietary study of Fukushima et al. (1973), correlation was attempted between proteinuria and glucosuria in Fuchu area villages and cadmium in the rice, particularly non-glutinous rice. In 37 villages studied, response rate (proteinuria and glucosuria) was seen to increase with increasing cadmium levels in rice, a significant correlation coefficient of 0.62 being obtained.

Earlier studies of existing proteinuria in Itai-Itai patients and other subjects from the Fuchu area involved rather unspecific (Friberg, et al., 1974) total protein methods. More recently, attention has focused on the levels of specific types of urinary proteins which may be more pathognomonic for cadmium's renal effects. This has also been discussed in the Renal Effects section.

One argument which has persisted in defense of the notion that Itai-Itai disease is not cadmium-based is the fact that Itai-Itai disease appears to be confined to the Jintsu River basin, although a number of other main cadmium-polluted areas exist. In 1975, Nogawa et al. claimed to have identified five cases of Itai-Itai disease among women in the Ichi River basin. All of these patients showed biochemical and other clinical evidence for the renal and bone damage sequelae associated with the malady. Autopsy data in one case were also consistent with the earlier data from the Jintsu River basin. Furthermore, the favorable response of three of these subjects to large doses of Vitamin D therapy parallels that seen in other victims of the disease.

In the Sub-Cellular Effects section, it has already been noted that chromosomal aberrations occur in individuals with Itai-Itai disease (vide supra).

In viewing the data available for Itai-Itai disease, one is struck by the fact that many early clinical investigators have restricted themselves to the extreme clinical phase of the continuum of changes accompanying chronic exposure. Fortunately, this problem is now being assessed more comprehensively and uniformly.

3.4.2. Epidemiological Studies of Other Cadmium-Polluted Areas in Japan

Japanese areas where epidemiological studies have also been carried out include Ikuno, Tsushima, Kakehoshi, Bandai, Annaka, Omuta, and Uguisuzawa; and reviews of these data have been carried out (Friberg et al., 1974).

In a more recent rather detailed report, Kjellström (1976) has reviewed and critiqued these areas of cadmium exposure in Japan where systemic effects such as proteinuria have been considered from the standpoint of dose-effect/dose-response relationships of cadmium.

The extent to which data comparisons can be made is restricted somewhat by the fact that proteinuria has been assessed in different ways, and not all factors have been matched in selecting control groups.

In 1972, a study was carried out involving 1560 individuals from the Ichi River basin in Hyogo prefecture, an area where the likelihood of pollution extends back for several centuries. Three control-area groups of 1574, 2002, and 638 persons were also employed (Watanabe et al., 1973). The corresponding proteinuria prevalence rates (determined by the sulfo salicyclic acid method) were 58, 33, 4, and 9 percent, respectively. Differences in these groups may be confounded by the fact that not all control areas used the same protein analysis technique. In a later study, Watanabe and Murayama (1974) found elevated β_2-microglobulin and lysozyme in urines of individuals from the most heavily exposed group (H area). It was in this same area that Nogawa et al. (1975) later reported five cases of Itai-Itai disease (vide supra).

Another zinc mine which was probably a long-term pollution source spanning several centuries has figured in the occurrence of significantly increased proteinuria in the Tsushima area of Nagasaki prefecture.

In the four villages of the Kakehoshi area in Ishikawa prefecture where cadmium pollution occurred from two long-active copper mines, a study of Ishizaki (1972) turned up proteinuria prevalence ranging from 39 percent for the worst exposure to 30, 28, and 22 percent for the others. No control group was employed in this study.

Japanese population groups in the areas of zinc smelters have also been studied. In the Bandai area of Fukushima prefecture, the site of a zinc smelter, a study (Fukushima Prefecture, 1971) of 1324 men and women over 30 years of age in the pollution belt using 215 women in a control area indicated that the prevalence of proteinuria was 12.3 percent compared to 4.7 percent in the control area.

Another site for a zinc smelter is the Annaka area of Gumma prefecture. While a study of 2397 persons (men and women, more than 30 years of age) in the polluted area showed a prevalence of proteinuria (12.1 percent) not materially different from that of a group of 895 controls (Kakinuma et al., 1971) as described in Friberg et al. (1974). These findings have been later ascribed to the brevity of the significant exposure period, only over the last decade (Kjellström, 1976).

The most recent study of the prevalence of proteinuria in the zinc-smelter area in the Omuta area (Friberg et al., 1974) showed a rate of 18.2 percent for the polluted area versus a rate of 6.8 percent for controls.

Saito et al. (1977) carried out a detailed study of proteinuria in the Hosogae area of Akita prefecture which is adjacent to a major copper refinery

operating for the past century, these studies spanning 1972 to 1975. These workers found that 13 to 22 percent of the area's population over 35 years old had proteinuria and glucosuria versus the general occurrence of 20 percent in all of Japan. Also, the levels of urinary β_2-microglobulin in this group increased with age and length of residence in this area.

Extensive soil contamination and a high contamination of rice are present in this area. In the studies of Watanabe et al. (1973), noted above in connection with proteinurea, urinary cadmium levels were related to the village average rice cadmium levels; adults excreted ca. 7 μg cadmium/liter at rice levels of 0.4 μg/g and this value rose to ca. 14 μg/liter at 1.1 μg/g in rice. These values correspond to 240 and 660 μg daily of cadmium intake. Kjellström (1977) found that women aged 50-59 and having long-term cadmium intake had blood levels of ca. 3 μg/dl and 24 hour excretion levels of ca. 15 μg. These latter values can be compared to calculated data, based on a 600 μg cadmium intake value, of 3.4 μg/dl blood and 14 μg/24 hour urine respectively (Kjellström and Nordberg, 1978).

3.5 EPIDEMIOLOGY OF CADMIUM, HYPERTENSION, AND CARDIOVASCULAR DISEASES

Hammer et al. (1972) presented a review of the information about the relationship of cadmium and hypertension and presented data to support some of their criticisms of the approaches taken by earlier investigators. Essentially they questioned the "single cause" approach pointing out that, particularly for conditions of high prevalence, this approach has inevitably failed. Much of the more recent work has proven them right in this contention. Investigators who have controlled for smoking status have found that the association of higher cadmium concentrations and hypertension is not independent.

Thind et al. (1976) and Glauser et al. (1976) found significantly higher cadmium concentrations in blood of hypertensive patients than in normotensive controls, but neither of these groups of investigators controlled for smoking status. Beevers et al. (1976a) found not only no difference for cadmium concentrations for hypertensives and normotensives but instead did find that smokers and non-smokers, regardless of pressure, showed differences in cadmium concentrations. A further report from this team (Beevers et al., 1976b) indicates that higher concentrations of lead were found in blood of male hypertensives than that of male normotensives. A difference in the same direction but not statistically significant was found for female patients and controls. These subjects came from the same area and clinic as those examined in the earlier study. The authors concluded that the findings of an association of hypertension and blood lead concentration is due to the quality of the tap water since this area has high lead levels in its drinking water. The case for an association for cadmium and hypertension appears weakened by this finding.

Autopsy studies were conducted by Ostergaard (1977a,b) and by Syverson et al. (1976). These investigators controlled for smoking and found no differences, Ostergaard (1977a,b) reporting higher levels among normotensives who smoked than among hypertensives. The reports from the North Carolina study (Shuman et al., 1974; Voors and Shuman, 1975) did not control for smoking. They found a statistically significant association for zinc concentrations in kidney tissue, and an association, consequently, for zinc-cadmium ratio, but not for cadmium concentrations per se.

The association of hypertension and hard water and associated levels of cadmium in water has been discussed by Perry et al. (1974). There is no

firm evidence as to the significance of this variable. Rather, the current available data is not definitive and can best be characterized as inconclusive and requiring further research.

Early studies by Hunt et al. (1971) and Hickey et al. (1967) related mortality rates to air cadmium levels. These statistical approaches use total mortality experience without taking account of population characteristics such as age distributions. Further, they do not take into account the fact that cadmium in air is not so ubiquitous as other pollutants, and single measures for air concentrations for entire populations are of dubious value.

Bierenbaum et al. (1975a,b) analyzed cardiovascular/renal mortality in populations with hard and soft water as well as different levels of cadmium concentrations in water using the Missouri and Kansas populations of the Kansas City metropolitan area. The investigators found higher mortality for the hard-water area of Kansas than Missouri. Two matched groups of 260 adult volunteers, one each from the two areas, were examined for blood pressure, electrocardiographic findings, selected serum-lipids, uric acid, and angina. Some statistical differences for the two groups were found, but smoking status was not controlled for. The significance of their finding must be questioned.

Autopsy studies reported by Voors et al. (1975) and Shuman et al. (1974) found an association for cadmium concentration in liver and death from heart disease. Syverson et al. (1976) found neither an association for cardiovascular disease nor for hypertension as discussed above.

The evidence for an association between cadmium and cardiovascular disease is no clearer than that for hypertension. The groups studied are

either extremely small or, if larger, were not controlled for relevant factors. It is impossible at this time either to rule out the postulated relationship or to confirm it.

3.6 EPIDEMIOLOGICAL STUDIES OF THE RESPIRATORY TRACT

The studies relating to the diseases of the lungs, other than cancer, almost universally concern occupationally exposed workers and have been reported elsewhere (Health Effects). Briefly, Lauwerys et al. (1974), Scott et al. (1976), and Smith et al. (1976a) found decreased pulmonary function in workers exposed to high air cadmium concentrations for long periods. Scott et al. (1976) also reported "restrictive airway disease" to be prevalent to a greater degree in the most exposed group. Smith et al. (1976a) found mild and moderate interstitial fibrosis in the group with high exposure.

Morgan et al. (19710 compared the tissue cadmium concentrations of autopsied patients grouped by cause of death. Cadmium concentration in liver was significantly higher in the group with the diagnosis of emphysema. A second group with a combined diagnosis of cancer of the lung and emphysema showed significantly higher cadmium concentrations for both liver and kidney. Smoking was not controlled for even though the investigators attempted to collect this information. Occupational exposure was reported for 23 percent of the "emphysema only" group, but only 4 and 5 percent of the "lung cancer" and "emphysema and lung cancer" groups had such exposures. These authors stressed that the findings are only suggestive. Similar distributions of mean values for zinc concentrations in liver and kidney suggest that it is by no means possible to implicate

cadmium as a single etiological factor. The cadmium/zinc ratio was not determined.

While there is no question that occupational exposure at high levels produces decreased pulmonary function, restrictive airway disease, interstitial fibrosis, and emphysema, no good evidence exists at present as to the effects of gradients of exposure levels for "normal" populations without high levels of occupational exposure.

3.7 CADMIUM AND CANCER

The investigations of causes of death among workers are one source of data; studies of tissue concentrations by cause of death are another major group. The data are sparse and subject to the limitations of retrospective study design and autopsy studies.

Potts (1965) conducted a health survey in an English alkaline-battery factory where source data for cadmium concentrations in air was available. The plant had been in operation for over 40 years, and the health status of past and present workers was assessed. There were 74 workers who had had exposures of more than 10 years, and 8 of these had died. Among these deaths, five were from cancer; and three of these were cancer of the prostate. These eight had worked at the plant when exposure levels had been high and before moving into a new building where air levels were much improved and where measures continued to be taken to achieve further reductions. Potts' report did not give enough information to interpret his striking finding in relation to mortality in the general population, and he presented no data for causes of deaths among workers with less than ten years' exposure. Also not clear is the reliability of establishing the base of 74 workers with ten or more years of exposure.

Kipling and Waterhouse (1967) reported a further study of the workers in this battery plant. They had extended the search for causes of death to all those with at least one year's exposure. They found 248 workers with this exposure with a total of 12 deaths from cancer in this group. Among these 12, four were cancer of the prostate. (Three among these were also included in Potts' findings). Mortality experience in an unidentified population stated to be similar was used to calculate expected numbers of deaths for all cancers and for specific cancer sites. For the four cancer sites, and for cancers for all sites, significant differences between observed and expected numbers of deaths were found only for cancer of the prostate.

The next relevant study of occupationally exposed workers was reported for workers at a cadmium smelter in the United States. Lemen et al. (1976) used employment histories to establish a population of 292 workers with more than two years' exposure which were a cohort for employment during a 30-year employment period between January, 1940, and December, 1969. Very thorough investigation produced information on vital status. It was found that, by 1974, 92 had died, 180 were known to be alive, and 20 were lost to observation. Causes of death were established and standardized mortality ratios (SMR) were calculated so that excessive risk could be analyzed. Mortality from cancer at all sites was found to exceed the expected number of cancer deaths by a statisticallly significant margin. Among the deaths from cancer, 12 were from sites in the respiratory system; and this observed number also gave a significant excess with an SMR of 235. Cancer of the prostate was also found to have a significantly increased risk

among these workers. The latency period for prostatic cancer deaths found both by Potts (1965) and Kipling and Waterhouse (1967) is 20 years or more. Lemen et al. (1976) found the same latency period. It should be kept in mind that the Lemen et al. (1976) study did not control for smoking.

A study of mortality among rubber workers was conducted by McMichael et al. (1976). This study was not confined to workers exposed to cadmium alone, and it is therefore not possible to implicate cadmium specifically in the mortality from cancers that was found. Cancer of the prostate showed an SMR of 119, which was only slightly elevated. A more detailed analysis of the specific jobs of these prostatic cancer deaths showed that workers in compounding and mixing areas and maintenance workers had a higher risk for this cancer. No air cadmium levels at the various work-sites were determined. These specific mixing jobs expose workers to cadmium and other metal oxides.

The evidence for cancer of the prostate is strongly suggestive but inconclusive at this time.

Autopsy studies have compared cadmium concentrations in tissues by causes of death. Lewis et al. (1972) found in their 172 autopsies that higher concentrations of cadmium in kidney cortex, liver, and lungs were found in cases of death from cancer of the bronchus and lungs. However, when cigarette smoking is controlled for, these differences disappear. This forces reconsideration of the findings reported earlier by Morgan et al. (1970, 1971), who found significantly higher cadmium tissue content for causes of death from cancer of the lung but did not control for smoking

status. Voors et al. (1975) reported on their autopsy series that they found no association for higher cadmium tissue concentrations and deaths from cancer.

Kolonel (1976) reported on a survey of patients at Roswell Park Memorial Institute for an 8-yr period, 1957 to 1964. All white males aged 50 to 79 yr with a diagnosis of renal cancer were compared to two control groups: one of all comparable males with non-malignant diagnoses and the second of males with cancer of the colon. From the smoking and employment histories all subjects were categorized as "exposed" or "not exposed" via the respiratory route. Data from the dietary history were used to categorize the men as nutritionally "exposed" or not. Two sources of respiratory exposure and the dietary exposure were therefore considered. Relative risk for cancer of the rectum was increased only when smoking and occupation were considered together when the age-specific, relative risk increase was found to increase to 4.4, yielding an excessive relative risk of 3.4.

There seems to be good suggestive evidence that cadmium may be a factor in cancers of various sites, but the association is by no means a simple one, particularly not at low or "normal" levels of exposure. It is important to note the excessive mortality or risk of mortality from cancer of the prostate is reported from two works where the chemical forms of cadmium differed. The evidence for cancer of the lung has been found in one study but was not confirmed in others. While the carcigenicity of cadmium is not firmly established, neither can it be dismissed. The U.S. Environmental Protection Agency's Carcinogen Assessment Group, in 1977, and the WHO International Agency for Research on Cancer (IARC)

monograph (1976) for cadmium reached the same conclusion in regard to occupational exposures and risk for cancer.

3.8 EPIDEMIOLOGICAL STUDIES RELATING TO CHROMOSOMAL ABNORMALITIES

A number of studies addressing the question of chromosomal abnormalities in humans and involving various exposure conditions have been reported. Shiraishi (1975) pointed out the occurrence of a number of chromosomal abnormalities in patients with Itai-Itai disease. Other studies touching on this issue are considred here.

In a study that also included Itai-Itai patients, Bui et al. (1975) analyzed lymphocyte cultures from six female Itai-Itai patients, four control Japanese samples, five cadmium-exposed Swedish workmen, and three Swedish controls and were unable to see any significant differences within either of the two sets of groups. Interestingly, however, the Swedish groups showed a lower frequency of abnormal cells than either of the Japanese groups. It is unlikely that the greater time lag from collection to culture in the case of the Japanese samples (4 days) could constitute an artifact in these results, since these investigators had not experienced any time-dependent effect of culturing of this magnitude (4 days) in the past.

In the occupational exposure studies of DeKnudt and Leonard (1975) and Bauchinger et al. (1976), significant chromosomal abnormalities were observed. In the former study, where workmen were exposed to cadmium and lead via dust and fumes, yields of chromatid exchange, spiralization disturbance, chromosome translocation, and ring and dicentric chromosomes obtained were higher than in a group of control, low-cadmium-exposure

workmen. In the latter data (Bauchinger et al., 1976), chromosomal damage was mainly of the chromatid type. Confounding these results, of course, is the fact that lead exposure had also occurred, thus this toxin could not be ruled out as being the main factor or a cofactor operating synergistically with cadmium.

All of the various studies, considered collectively, indicate that the issue of cadmium as the etiological factor in chromosomal abnormalities is still open to controversy.

3.9 EPIDEMIOLOGICAL STUDIES OF OCCUPATIONAL EXPOSURE TO CADMIUM

A comprehensive review of all of the studies of occupational groups regarding the health effects of cadmium exposure is outside the purpose of this report. Where specific studies have been deemed appropriate to demonstrate the magnitude of cadmium's health effects in man, these data have been incorporated into the appropriate sub-sections of the Health Effects report.

For a more appropriate compendium in which occupational exposure is the chief emphasis, one is directed to the recent National Institute of Occupational Safety and Health's Criteria Document for Cadmium (NIOSH, 1976).

3.10 REFERENCES FOR CHAPTER 3

Bauchinger, M., E. Schmid, H. J. Einbrodt, and J. Dresp. Chromosome aberrations in lymphocytes after occupational exposure to lead and cadmium. Mutat. Res. 40:57-62, 1976.

Beevers, D. G., B. C. Campbell, A. Goldberg, M. R. Moore, and V. M. Hawthorne. Blood-cadmium in hypertensives and normotensives. Lancet 2:1222-1224, 1976a.

Beevers, D. G., E. Erskine, M. Robertson, A. D. Beattie, B. C. Campbell, A. Goldberg, M. R. Moore, and V. M. Hawthorne. Blood-lead and hypertension. Lancet 2:1-3, 1976b.

Bierenbaum, M. L., A. I. Fleishman, J. Dunn, and J. Arnold. Possible toxic water factor in coronary heart disease. Lancet 1:1008-1010, 1975a.

Bierenbaum, M. L. Reply to Sharrett and Feinleib. Lancet 2:76, 1975b.

Bogden, J. D., N. P. Singh, and M. M. Joselow. Cadmium, lead, and zinc concentrations in whole blood samples of children. Environ. Sci. Technol. 8:740-742, 1974.

Bui, T. H., J. Linsten, and G. F. Nordberg. Chromosome analysis of lymphocytes from cadmium workers and Itai-Itai patients. Environ. Res. 9(2):187-195, 1975.

Carcinogen Assessment Group's Assessment of Carcinogenic Risk from Population Exposure to Cadmium in the Ambient Air. External review draft. U.S. Environmental Protection Agency, Office of Research and Development, Washington, D.C. May, 1978.

Clausen, J., and S. C. Rastogi. Heavy metal pollution among autoworkers. II. Cadmium, chromium, copper, manganese, and nickel. Br. J. Ind. Med. 34:216-266, 1977a.

Clausen, J., and S. C. Rastogi. Heavy metal pollution among auto workers. I. Lead. Br. J. Ind. Med. 34:208-215, 1977b.

Creason, J. P., T. A. Hinners, J. E. Bumgarmer, and C. Pinkerton. Trace elements in hair, as related to exposure in metropolitan New York. Clin. Chem. 21(4):603-612, 1975.

Creason, J. P., D. I. Hammer, A. V. Colucci, L. Priester, and J. Davis. Blood trace metals in military recruits. South. Med. J. 69(3): 289-293, 1976.

Deknudt, G., and A. Leonard. Cytogenetic investigations on leucocytes of workers from a cadmium plant. Environ. Physiol. Biochem. 5: 319-327, 1975.

Delves, H. T., B. E. Clayton, and J. Bicknell. Concentration of trace metals in the blood of children. Br. J. Prev. Soc. Med. 27: 100-107, 1973.

Ediger, R. D., and R. L. Coleman. Determination of cadmium in blood by a Delves cup technique. Atom. Absorp. Newslett. 12(1):3-6, 1973.

Einbrodt, H. J., J. Rosmanith, and D. Projsnar. Der Cadmiumgehalt im Blut und Rauchgewohnheiten. Naturwissenschaften 63:148, 1976.

Elinder, C.-G., T. Kjellström, L. Linnman, and G. Pershagen. Urinary excretion of cadmium and zinc among persons from Sweden. Environ. Res. 15:473-484, 1978.

Elinder, C.-G., T. Kjellström, L. Friberg, B. Lind, and L. Linnman. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Arch. Environ. Health 31:292-302, 1976.

Friberg, L., M. Piscator, G. F. Nordberg, and T. Kjellström. Cadmium in the Environment. CRC Press, Cleveland, 1974.

Friberg, L., T. Kjellström, G. Nordberg, and M. Piscator. Cadmium in the Environment - III. A Toxicological and Epidemiological Appraisal. EPA-650/2-75-049. U.S. Environmental Protection Agency, Washington, D.C., 1975.

Fukabori, S., and K. Nakaaki. Urinary excretion of cadmium, lead, mercury, and fluorine. Rodo Kagaku 50(4):249-269, 1974.

Fukushima, I. Cadmium content in the basin of the rivers Usui and Watangse in Gumma Prefecture and its health effect on the inhabitants. In: Kankyo Hoken Report No. 24. Japanese Association of Public Health, Tokyo, 1973. pp. 131-135.

Fukushima Prefecture. Result of the Health Examination on Inhabitants of the Observation Area for Environmental Pollution of Cadmium. Fukushima, Japan, March 1971.

Fukuyama, Y. Proteinuria in Itai-Itai disease and cadmium poisoning. Igaku To Seibutsugaku 84:41-46, 1972.

Fulkerson, W., and H. E. Goeller. (eds.). Cadmium, the Dissipated Element. ORNL-NSF-EP-21. Oak Ridge National Laboratory, Oak Ridge, TN, 1973.

Glauser, S. C., C. T. Bello, and E. M. Glauser. Blood-cadmium levels in normotensives and untreated hypertensive humans. Lancet 1: 717-718, 1976.

Gross, S. B., D. W. Yeager, and M. S. Middendorf. Cadmium in liver, kidney, and hair of humans, fetal through old age. J. Toxicol. Environ. Health 2:153-167, 1976.

Hambidge, K. M., P. Walravens, V. Kumar, and C. Tuchinda. Chromium, zinc, manganese, copper, nickel, iron and cadmium concentrations in the hair of residents of Chandigarh, India, and Bangkok, Thailand. In: Trace Substances in Environmental Health, D. D. Hemphill. (ed.). University of Missouri Press, Columbia, MO, 1972. pp. 39-44, 1974.

Hammer, D. I., J. F. Finklea, J. P. Creason, S. H. Sandifer, J. E. Keil, L. E. Priester, and J. F. Stara. Cadmium exposure and human health effects. In: Trace Substances in Environmental Health. D. D. Hemphill. (ed.). University of Missouri Press, Columbia, MO, 1972. pp. 269-283.

Hammer, D. I., J. F. Finklea, R. H. Hendricks, C. M. Shy, and R. J. M. Horton. Hair trace metal levels and developmental exposure. Am. J. Epidemiol. 93(2):84-92, 1971.

Harvey, T. C., J. S. McLellan, B. J. Thomas, and J. H. Fremlin. Measurement of liver-cadmium concentrations in patients and industrial workers by neutron-activation analysis. Lancet 1:1269-1272, 1975.

Hecker, L. H., H. E. Allen, B. D. Dinman, and J. V. Neil. Heavy metal levels in acculturated and unacculturated populations. Arch. Environ. Health 29(4):81-185, 1974.

Hickey, R. J., E. P. Schoff, and R. C. Clelland. Relationship between air pollution and certain chronic disease death rates. Multivariate statistical studies. Arch. Environ. Health 15:228-238, 1967.

Hunt, W. F., Jr., C. Pinkerton, O. McNulty, and J. Creason. A study in trace element pollution of air in 77 midwestern cities. In: Trace Substances in Environmental Health. D. D. Hemphill. (ed.). University of Missouri Press, Columbia, MO, 1971. pp. 56-58.

Imbus, H. R., J. Cholak, L. H. Miller, and T. Sterling. Boron, cadmium, chromium, and nickel in blood and urine. A survey of American working men. Arch. Environ. Health 6:112-121, 1963.

International Agency for Research on Cancer, Monographs on the evaluation of the Carcinogenic Risk of Chemicals to Man: Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Anesthetics, Vol. II. World Health Organization, Lyon, 1976, pp. 39-74.

Ishizaki, A. About the result of a health examination. In: Kankyo Hoken Report No. 11. Japanese Association of Public Health, Tokyo, 1972. pp. 27-30.

Johnson, D. E., J. B. Tillery, J. M. Hosenfeld, and J. W. Register. Development of Analytic Techniques to Measure Human Exposure to Fuel Additives. EPA-650/1-74-003. U.S. Environmental Protection Agency, Washington, D.C., 1974.

Johnson, D. E., J. B. Tillery, and R. J. Prevost. Trace metals in occupationally and nonoccupationally exposed individuals. Environ. Health Persp. 10:151-158, 1975.

Johnson, D. E., R. J. Prevost, J. B. Tillery, and R. E. Thomas. The Distribution of Cadmium and Other Metals in Human Tissue. Final Report, Contract No. 68-02-1725. U.S. Environmental Protection Agency, Washington, D.C., 1977.

Kakinuma, K., K. Shimizu, M. Sugareda, Y. Akita, Y. Takiyama, I. Fukushima, K. Sugimaira, A. Fujii, K. Sakamura, N. Nagata, and T. Tsuji. About the prevalence of proteinuria as well as a result of a health examination of the inhabitants along the Usuigawa River. Meeting of the Japanese Association of Public Health, November, 1971.

Kipling, M. D., and J. A. H. Waterhouse. Cadmium and prostatic carcinoma. Lancet. 1:730-731, 1967.

Kjellström, T. Epidemiological evaluation of proteinuria in long-term cadmium exposure with a discussion of dose-response relationships. In: Effects and Dose-Response Relationships of Toxic Metals. G. F. Nordberg. (ed.) Elsevier, Amsterdam, 1976. pp. 309-330.

Kjellström, T., K. Shiroishi, and P.-E. Evrin. Urinary β_2- excretion among people exposed to cadmium in the general environment. Env. Res. 13:318-344, 1977.

Kjellström, T., and G. F. Nordberg. A kinetic model of cadmium metabolism in the human being. Environ. Res. 16:248-269, 1978.

Kolonel, L. N. Association of cadmium with renal cancer. Cancer 37(4): 1782-1787, 1976.

Kubasik, N. P., and M. T. Volosin. A simplified determination of urinary cadmium, lead, and thallium, with use of carbon rod atomization and atomic absorption spectrophotometry. Clin. Chem. 19(9):954-958, 1973.

Kubota, J., V. A. Lazar, and F. Loese. Copper, zinc, cadmium and lead in human blood from 19 locations in the U.S. Arch. Environ. Health 16:788-793, 1968.

Lauwerys, R. R., J.-P. Buchet, and H. A. Roels. Comparative study of effect of inorganic lead and cadmium on blood δ-aminolevulinate dehyratase in man. Br. J. Ind. Med. 30:359-364, 1973.

Lauwerys, R. R., J.-P. Buchet, H. A. Roels, J. Brouwers, and D. Stanescu. Epidemiological survey of workers exposed to cadmium. Arch. Environ. Health 28:145-148, 1974.

Lemen, R. A., J. S. Lee, J. K. Wagoner, and H. P. Blejer. Cancer mortality among cadmium production workers. Ann. N.Y. Acad. Sci. 271:273-279, 1976.

Lewis, G. P., W. J. Jusko, and L. L. Coughlin. Cadmium accumulation in man: Influence of smoking, occupation, alcoholic habit and disease. J. Chronic Dis. 25:717-726, 1972.

Lewis, G. P., W. J. Jusko, L. L. Coughlin, and S. Hartz. Contribution of cigarette smoking to cadmium accumulation in man. Lancet 1:291-292, 1972.

McKenzie, J. M., and J. D. Neallie. Cadmium in urine and hair from New Zealand adults. In: Trace Substances in Environmental Health. D. D. Hemphill, (ed.), University of Missouri Press, Columbia, MO, 1974. pp. 45-48.

McMichael, A. J., D. A. Andejelkovic, and H. A. Tyroler. Cancer mortality among rubber workers. An epidemiological study. Ann. N.Y. Acad. Med. 271:125-137, 1976.

Miller, G. J., M. J. Wylie, and D. McKeown. Cadmium exposure and renal accumulation in an Australian urban population. Med. J. Austral. 1:20-23, 1976.

Morgan, J. M. Cadmium and zinc abnormalities in bronchogenic carcinoma. Cancer 25(6):1394-1398, 1970.

Morgan, J. M., H. B. Burch, and J. B. Watkins. Tissue cadmium and zinc content in emphysema and bronchogenic carcinoma. J. Chronic Dis. 24:107-110, 1971.

National Institute for Occupational Safety and Health. Criteria for a Recommended Standard. Occupational Exposure to Cadmium. HEW Publication No. (NIOSH) 76-192, U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, Cincinnati, Ohio, August, 1976.

Norgawa, K., A. Ishizaki, M. Fukushima, I. Shibata, and N. Hagino. Studies on the women with acquired Fanconi syndrome observed in the Ichi River basin polluted by cadmium. Is this Itai-Itai disease? Environ. Res. 10:280-307, 1975.

Nygaard, S.-P., G. J. Bende, and J. C. Hansen. Normal levels of lead and cadmium in human blood. Nord. Hyg. Tidskr. 54:153-162, 1974.

Ostergaard, K. Cadmium and hypertension. Lancet 1:677-678, 1977a.

Ostergaard, K. The concentration of cadmium in renal tissue from smokers and nonsmokers Acta Med. Scand. 202:193-195, 1977b.

Perry, H. M., and E. F. Perry. Possible relationships between the physical environment and human hypertension: Cadmium and hard water. Prev. Med. 3:344-352, 1974.

Pinkerton, C., J. P. Creason, D. I. Hammer, and A. V. Colucci. Multimedia indices of environmental trace-metal exposure in humans. In: Proceedings of the 2nd International Symposium on Trace Element Metabolism in Animals, 1973. Baltimore, University Park Press, 1974. pp. 465-469.

Piscator, M., T. Kjellstrøm, and B. Lind. Contamination of cigarettes and pipe tobacco by cadmium-oxide dust. Lancet 2:587, 1976.

Potts, C. L. Cadmium proteinuria--The health of battery workers exposed to cadmium oxide dust. Ann. Occup. Hyg. 8:55-61, 1965.

Roels, H., R. Lauwerys, D. Materne, and J. P. Buchet. Study on cadmium proteinuria. Glomerular dysfunction: An early sign of renal impairment. In: Proceedings International Symposium. Recent Advances of the Health Effects of Environmental Pollution. Volume II. Commission of the European Communities, Luxembourg, 1975. pp. 631-641.

Rosmanith, J., H. J. Einbrodt, and T. Gordon. Relationships between immissions of plumb and zinc and the levels of plumb, zinc, and cadmium in blood, urine and hair in children. Zentralbl. Bakteriol. Parasitenkd. Infektionskr. Hyg. Abt. 1: Orig. Reihe B: 161:125-136, 1975.

Rosmanith, J., H. J. Einbrodt, and W. Ehm. To the behavior of cadmium and lead with a different cadmium or lead burden. Zentralbl. Bakteriol. Parasitenkd. Infektionskr. Hyg. Abt. 1: Orig. Reihe B: 165:207-225, 1977.

Ross, R. T., and J. G. Gonzalez. The direct determination of cadmium in biological samples by selective volatilization and graphic tube reservoir atomic absorption spectrometry. Anal. Chim. Acta 70:443-447, 1974.

Saito, H., R. Shioji, Y. Hurukawa, K. Nagai, T. Arikawa, T. Saito, Y. Sasaki, T. Furuyama, and K. Yoshinaga. Cadmium-induced proximal tubular dysfunction in a cadmium-polluted area. Contr. Nephrol. 6:1-12, 1977.

Scott, R., E. A. Mills, G. S. Fell, F. E. R. Husian, A. J. Yates, P. J. Paterson, A. McKirdy, J. M. Ottoway, O. P. Fitzgerald-Finch, A. Lamont, and S. Roxburgh. Clinical and biochemical abnormalities in coppersmiths exposed to cadmium. Lancet 2:396-398, 1976.

Shiraishi, Y. Cytogenetic studies in 12 patients with Itai-Itai disease. Humangenetik 27(1):31-44, 1975.

Shiroishi, Y., and T. H. Yoshida. Chromosomal abnormalities in cultured leucocyte cells from Itai-Itai disease patients. Proc. Jpn. Acad. 48:248-251, 1972.

Shuman, M. S., A. W. Voors, and P. N. Gallagher. Contribution of cigarette smoking to cadmium accumulation in man. Bull. Environ. Contam. Toxicol. 12(5):570-576, 1974.

Smith, T. J., T. L. Petty, J. C. Reading, and S. Lakshminarayan. Pulmonary effects of chronic exposure to airborne cadmium. Am. Rev. Respir. Dis. 114:161-169, 1976a.

Smith, T. J., A. R. Temple, and J. C. Reading. Cadmium, lead, and copper blood levels in normal children. Clin. Toxicol. 9(1):75-87, 1976b.

Stoeppler, M., F. Backhaus, R. Dahl, M. Dumont, H. Hagedorn-Gotz, K. Hilpert, P. Klahre, H. Rutzel, P. Valenta, and H. W. Nurnberg. Zur blei-und cadmiumanalytik in biologischen matrices. In: Proceedings International Symposium. Recent Advances in the Assessment of the Health Effects of Environmental Pollution. Volume IV. Commission of the European Communities, Luxembourg, 1975. pp. 2231-2245.

Syverson, T. L. M., T. K. Stray, G. B. Syverson, and J. Ofstad. Cadmium and zinc in human liver and kidney. Scand. J. Clin. Lab. Invest. 36(3):251-256, 1976.

Tada, O., K. Nakaaki, and S. Fukabori. Urinary excretion of lead, mercury, cadmium, and fluoride in normal subjects. J. Sci. Labour. 48:14-18, 1972.

Taguchi, T., T. Suzuki, S. Suzuki, and T. Takemoto. Variation in daily urinary excretion of lead, cadmium, δ-aminolevulinic acid and coproporphyrin in 5 men without occupational exposure to metals. Ind. Health 10:77-83, 1972.

Tati, M., Y. Katagiri, and M. Kawai. Urinary and fecal secretion of cadmium in normal Japanese: An approach to non-toxic levels of cadmium. In: Effects and Dose-Response Relationships of Toxic Metals. G. F. Nordberg. (ed.). Elsevier, Amsterdam, 1976. pp. 333-342.

Thind, G. S., and G. M. Fischer. Plasma cadmium and zinc in human hypertension. Clin. Sci. Mol. Med. 51:483-486, 1976.

Tsuchiya, K., Y. Seki, and M. Sugita. Cadmium concentrations in the organs and tissues of cadavers from accidental death. Keio J. Med. 25:83-90, 1976.

Ulander, A., and O. Axelson. Measurement of blood-cadmium levels. Lancet 1:682-683, 1974.

Voors, A. W., and M. S. Shuman. Liver cadmium levels in North Carolina residents who died of heart disease. Bull. Environ. Contam. Toxicol. 17(6):692-696, 1977.

Voors, A. W., M. S. Shuman, and P. N. Gallegher. Atherosclerosis and hypertension in relation to some trace elements in tissues. World Rev. Nutr. Diet 20:299-326, 1975.

Watanabe, H., Y. Hasegawa, H. Murayama, N. Matsushita, E. Nagakura, T. Okuno, K. Ono, M. Araki, T. Ogawa, and Y. Teraoka. In: Kankyo Hoken Report No. 24. Japanese Association of Public Health, Tokyo, Japan. 1973. p. 122-130.

Watanabe, H., and H. Murayama. A study on health effect indices concerning population in cadmium-polluted area. In: Proceedings International Symposium Recent Advances in the Assessment of the Health Effects of Environmental Pollution. Volume I. Commission of the European Communities, Luxembourg, 1975. pp. 91-104.

Willden, E. G., and B. E. B. Hyne. Blood and urinary cadmium in chronic renal failure. Nephron 13(3):253-257, 1974.

World Health Organization Task Group on Environmental Health. Environmental Health Criteria for Cadmium: Summary. WHO, Geneva, 1977.

Wysowski, D. K., P. J. Landrigran, S. W. Ferguson, R. E. Fontaine, T. A. Tsongas, and B. Porter. Cadmium exposure in a community near a smelter. Amer. J. Epidiol. 107(1):27-35, 1978.

Zeilhuis, R. L., E. J. Stuik, R. F. M. Herber, H. J. A. Salle, M. M. Verberk, F. D. Posma, and J. L. Jager. Smoking habits and levels of lead and cadmium in blood in urban women. Int. Arch. Occup. Environ. Health 39:53-58, 1977.

4. HUMAN HEALTH RISK ASSESSMENT OF CADMIUM

4.1 INTRODUCTION

In several respects, cadmium is rather unique among those metallic elements that are toxic to man. Its very long biological half-life leads to a steady increase in body burden over an individual's lifetime. Unlike lead, however, cadmium accumulates in soft tissue, chiefly the kidney, and little of the body burden is deposited in bone where it might become inert. Furthermore, there is no treatment available to prevent the accumulation of cadmium in the kidney or to remove or eliminate cadmium stored in the kidney or other soft tissues. Also, the adverse physiological effects associated with cadmium are essentially irreversible in nature. Thus, the most effective approach in protecting against its toxicity appears to be minimization of exposure to the metal. These two factors provide a strong basis for advocating limitation of human exposure in order to forestall adverse effects that may not appear until late in an individual's lifespan.

In addition to the above points concerning cadmium, e.g., its insidious gradual tissue accumulation over long periods of time, it should be noted that, so far as can be discerned to date, cadmium possesses no particular physiological benefit for man. Thus, there is no health-risk/health-benefit balance to be considered in discussing the hazards to public health associated with environmental exposure to the element.

To assess the issue of risk to public health posed by cadmium exposure, two aspects of the problem must be considered: (1) sources and levels of exposure and (2) population response.

Key questions about the sources of exposure that must be considered include: (1) What are the environmental sources of cadmium exposure of present or potential future concern in the United States? (2) What are the various routes by which cadmium enters the body? The latter question is a particularly vexing one in the case of a multi-media contaminant such as cadmium. A primary route of entry into the environment can lead to secondary and tertiary contamination; e.g., airborne cadmium contributes via fallout to soil levels which in turn influence the levels of cadmium in plants, animals, and food.

Several crucial questions must be considered with respect to population response:

(1) What are the human biological and pathophysiological responses to cadmium observed at environmentally relevant cadmium exposure levels?

(2) Do there exist within the general population in the United States or elsewhere certain sub-groups at particular risk to the adverse health effects of cadmium, either by reason of a special exposure relationship or an abnormally vulnerable physiological status?

(3) Quantitatively, what is the magnitude of the risk in terms of numbers of individuals potentially exposed to levels of cadmium sufficient to induce particular adverse health effects?

The first question posed was partially answered in the previous sections on health effects of cadmium (Chapters 2 and 3). It requires expansion here, however, to more fully consider dose-effect and dose-response relationships for humans and to assess the utility of various indicators of exposure in evaluating the effects of different types of exposure.

To better understand this portion of the report, it would be helpful to define the various terms which will be encountered. "Dose" is the amount or concentration of a substance which is presented over time to the specific, intracellular site where the effect is imparted. Since it is not usually possible to assess directly the quantity of that substance in the living organism at the affected site ("effect site"), the external and internal doses are considered as indices mirroring the effect-site concentration. "External dose" is the amount of the toxic substance in the external environment (air, water, food, etc.) to which an organism is exposed. "Internal dose" is the absorbed portion of the substance and is an integrated reflection of all contributing external exposures.

"Effect" is a biological change resulting from exposure to a toxic substance. "Dose-effect relationship" is a quantitative relationship between the dose and a specific effect i.e., it reflects changes in the intensity of an effect as a function of variations in dose. Dose-effect relationships vary among members of a population, and the frequency at which this occurs is expressed as the dose-response relationship. "Response" specifically is defined by Nordberg (1976) as that proportion or percentage of a population that exhibits a specific effect at a given internal dose level.

Nordberg (1976) has defined the concept of critical organ, critical concentration in the critical organ, and critical effect. "Critical organ" is defined as that organ which first attains the critical concentration of a metal under defined situations and for a given population. The "critical concentration" is defined as the mean concentration of the toxic

substance in the critical organ at which adverse functional changes appear. The "critical effect" is the first adverse effect that occurs along the continuum of dose-effect relationships.

4.2 EXPOSURE ASPECTS

Cadmium, although a relatively rare metal, is widely distributed naturally in the Earth's crust, often in close association with zinc and other metals. It is, therefore, rather ubiquitously encountered in trace amounts as a geochemical component of many surface soils, in underground water tables, and in surface waterways. Substantial additional amounts of cadmium, however, are continuously added to the "natural" background levels of the element in soils and water as a consequence of anthropogenic activities. Thus, in industrialized societies such as the United States, considerable amounts of cadmium enter the environment as a result of the manufacture, use, or disposal of cadmium-containing products or waste materials. Since little or no recycling of cadmium occurs, its use is said to be dissipative, i.e., the amount entering the environment roughly equals the amount produced or used; and this steady accumulation in the environment is one factor of considerable concern in assessing the risk associated with cadmium exposure.

The current amount of cadmium entering the environment annually in the United States is variably estimated at about 2,000 to 5,000 tons, with the lower figure being based on limited measurements and estimates for 1974 (Sargent and Metz, 1975; Yost et al., 1975) and the higher figure being the most recent data available to the United States Environmental Protection Agency (U.S. EPA Atmospheric Cadmium: Population Exposure Analysis, 1978). The latter figure may be higher because its calculation involved the use of stack-test data rather than mass balances. Of these amounts, about 20

percent arose from zinc mining and smelting, 30 percent from industrial use of cadmium, and the rest from inadvertent sources, i.e., from municipal incineration of waste materials, fossil-fuel use, phosphate fertilizer use, and sewage-sludge disposal. Cadmium released into the environment through such activities can eventually affect humans via contamination of air, water, or soil. Of particular concern is the entry, from any of these media, of cadmium into the human food chain as illustrated in Figure 4.1, and in any consequent increase in exposure of humans to the metal.

Concisely discussed below are estimates of present cadmium levels encountered in air, water, soil, and food in the United States, along with major sources of cadmium contributing to existing levels of the metal in each of those media. Also discussed below are certain trends or factors that can be reasonably well discerned at this time as being potential future problems in terms of possibly contributing to increased cadmium exposures of human populations in the United States.

4.2.1 Ambient-Air levels of Cadmium

Widely varying amounts of cadmium have been detected in air over rural and urban areas around the world, with specific concentrations depending mainly on the degree of industrialization of a given region. In regard to natural background levels of cadmium in the ambient air, levels of atmospheric cadmium over remote rural areas and many small urban areas are usually very low and are often non-detectable. For example, numerous air sampling stations in small towns yielded frequent readings of 0.1 ng/m^3 or non-detectable values for cadmium in the air, as reported as part of the SAROAD data file, which compiles atmospheric data submitted by states (see EPA Multimedia Levels Cadmium, 1977, pp. 2-6 to 2-11). Thus, natural background levels

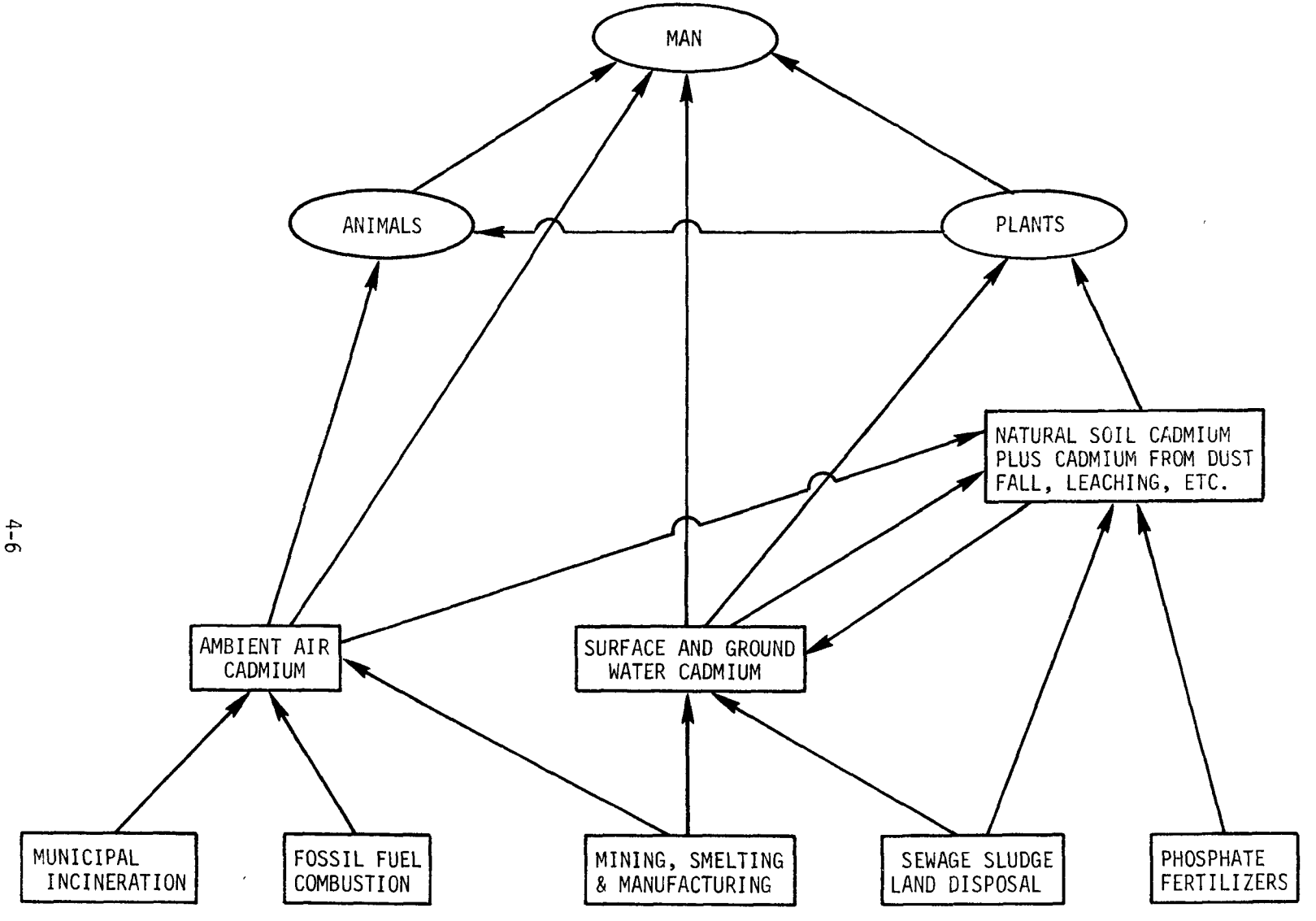


Figure 4-1. Diagrammatic representation of multi-media routes by which cadmium exposure of man can occur after dissipation of the element into the environment by anthropogenic activities.

for atmospheric cadmium appear to be definitely below 0.1 ng/m^3 and may even be essentially zero in the absence of contributions from man's activities.

In contrast to the above low, frequently non-detectable background levels of cadmium generally present in air over rural or small urban areas of the United States, considerably higher concentrations have been observed in ambient air over larger urban centers or industrialized rural areas. Of historical interest, among the highest ambient air levels recorded within the United States are readings of 0.12 μg/m^3 obtained in El Paso, Texas in 1964 and 0.300 to 0.489 μg/m^3 in Shoshone County, Idaho, in 1974. Other readings taken in the United States in a 1969 survey ranged from 0.006 μg/m^3 in San Francisco, California, to 0.036 μg/m^3 in St. Louis, Mo.; and a survey in 1970 produced comparable results (Friberg et al., 1974). Since 1970, further systematic air monitoring conducted by the EPA across the United States, yielded results as discussed below. That is, ambient air levels of cadmium monitored by the EPA National Air Surveillance Network (NASN), with inputs from state and local agencies, during 1970-1974 are presented in Table 4-1 (Akland, 1976). The table indicates that the average annual values for the U.S. cities listed fall mainly within a range of 0.001 to 0.020 μg/m^3, with a number of averages being below the limit of detection.

Exceptions to the above pattern are found in areas where zinc or lead mining and smelting is or has been conducted. In particular, values from Idaho and Montana have often been 0.100 μg Cd/m^3 or greater, as reported in the SAROAD file (U.S. EPA, Multimedia Levels Cadmium, 1977). Faoro and McMullen (1977), however, assembled a plot of the fiftieth percentile of annual

Table 4-1. ANNUAL AVERAGE URBAN ATMOSPHERIC CADMIUM CONCENTRATIONS REPORTED BY NATIONAL AIR SURVEILLANCE NETWORKS, 1970-1974[a]
(L.D. = Limit of Detection)

Location	Station number	Cadmium concentration, $\mu g/m^3$				
		1970	1971	1972	1973	1974
Arizona						
Douglas	01	---	---	0.0132	---	---
Tucson	01	0.0065	0.0251	0.0045[b]	0.0045[b]	0.0062[b]
Colorado						
Denver	01	0.0102	0.0101	---	---	---
Connecticut						
Bridgport	01	0.0117	---	0.0057	---	---
Waterbury	01	. 251	0.0048	0.0174	0.0027[b]	0.0139
Georgia						
Atlanta	01	---	0.0210	---	---	---
Illinois						
Chicago	01	L.D.	0.0065	0.0030[b]	---	---
East St. Louis	01	---	0.0045[b]	0.0052	---	---
Peoria	01	0.0067	---	---	---	---
Indiana						
East Chicago	01	0.0187	0.008[b]	---	---	0.0056
Indianapolis		0.0066	0.0063	0.009[b]	---	---
Kentucky						
Ashland	02	0.0108	---	0.0093	---	0.006[b]
Covington	01	0.0048[b]	0.0049	0.003[b]	---	L.D.
Louisiana						
New Orleans	02	L.D.	0.0184	L.D.	---	---
Shreveport	01	L.D.	0.0132	L.D.	---	L.D.
Maine						
Portland	02	L.D.	0.0086	---	---	---
Michigan						
Detroit	01	0.0047	L.D.	---	---	---
Grand Rapids	01	---	0.0116	L.D.	---	---
Minnesota						
St. Paul	01	0.0060	---	0.0086	---	---
Missouri						
St. Louis	01	---	0.0155	---	---	---
Montana						
Helena	01	---	0.150	---	---	---

Table 4-1 (cont.). ANNUAL AVERAGE URBAN ATMOSPHERIC CADMIUM CONCENTRATIONS REPORTED BY NATIONAL AIR SURVEILLANCE NETWORKS, 1970-1974[a]
(L.D. = Limit of Detection)

Location	Station number	Cadmium concentration, $\mu g/m^3$				
		1970	1971	1972	1973	1974
New Jersey						
Camden	01	0.0063	---	---	---	---
Elizabeth	02	---	0.0167	---	---	---
Jersey City	01	0.0081	0.0056	0.0124	---	---
Newark	01	0.0125	---	0.0159	---	0.0052
Perth Amboy	01	0.0055[b]	0.0128	0.0189	---	---
New York						
New York City	01	0.0071	---	0.0060	---	---
North Carolina						
Winston Salem	02	---	0.0076	---	---	---
Ohio						
Cincinnati	01	0.0086	---	---	---	---
Cleveland	01	0.0088	---	---	---	---
Youngstown	01	0.0056	---	---	---	---
Pennsylvania						
Allentown	01	0.0081	0.0042[b]	0.0178	0.0042[b]	0.0134
Bethlehem	02	0.0140	0.0191	0.0068[b]	0.0068	---
Hazleton	01	---	---	---	0.0065	---
Philadelphia	04	---	---	0.0057	---	0.0038[b]
Scranton	01	L.D.	0.0067	L.D.	---	L.D.
Texas						
El Paso	02	0.0618	---	0.0442	0.0206	0.0242
Virginia						
Lynchburg	01	0.0135	0.0040[b]	L.D.	---	---
Wisconsin						
Kenosha	01	---	L.D.	0.0143	---	---
Racine	01	L.D.	---	0.0071	---	---

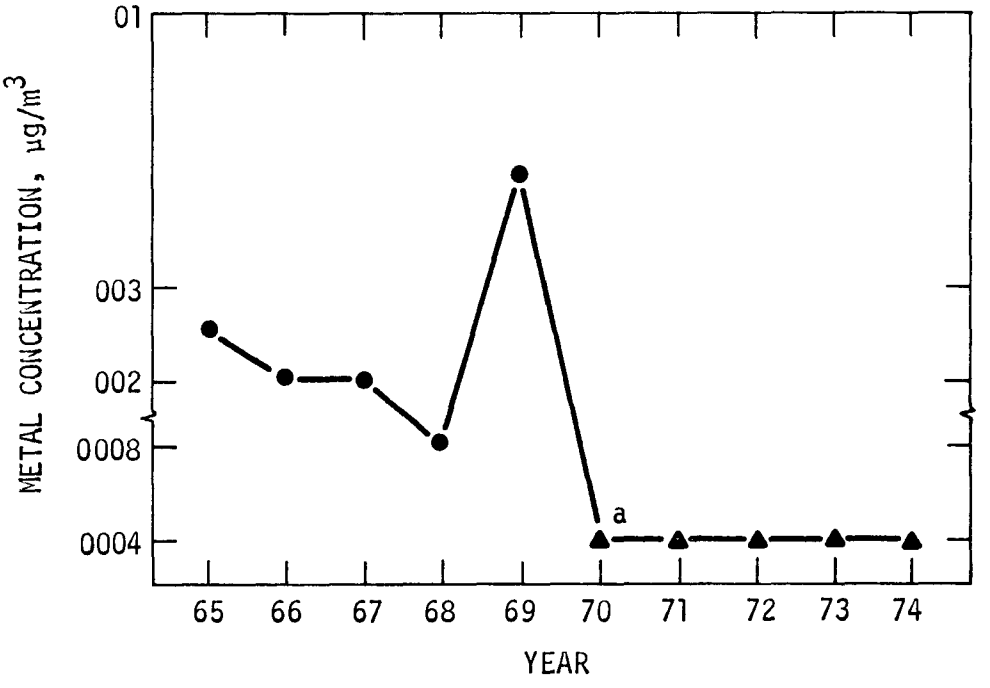
[a]Source: Akland, 1976.

[b]L.D./2 used for computation of annual average.

averages for cadmium associated with metal-industry sources at urban sites during the period of 1965-1974, in order to examine trends in levels of airborne cadmium in the United States (Figure 4-2); and it may be seen that there has been a definite large decrease in airborne cadmium emissions from industrial sources since 1970, with that trend toward lower emission levels expected to hold for the foreseeable future.

Municipal incineration of waste materials is yet another major source of cadmium emissions into the ambient air and may actually represent the single largest source of airborne cadmium exposure in terms of numbers of people directly affected and amount per year released into the atmosphere (i.e., about 131 tons annually). That is, it has been estimated that approximately 50,000,000 people are exposed to cadmium emitted by municipal incinerators, with the average exposure level being approximately 7 ng/m^3 (U.S. EPA, Atmospheric Cadmium Population Exposure Analysis, 1978). This includes cadmium emissions due both to general incineration of wastes and more specific sewage sludge incineration. It has been estimated, however, that future trends for cadmium emissions associated with both types of municipal incineration will not be toward increased emissions overall, since use of emission controls on the incinerators is expected to offset possible cadmium emission increases that would otherwise accompany increased incineration loads (U.S. EPA, Sources of Atmospheric Cadmium, 1978).

A third major source of cadmium input into the atmosphere is the combustion of fossil fuels. Coal-fired and oil-fired power plants, fuel oil, diesel oil, and gasoline have all been found to be responsible for some emission of airborne cadmium. While it is difficult to establish



[a]▲ Indicates value below lower discrimination limit.

Figure 4-2. Trends in 50th percentile of annual averages for cadmium associated with metal industry sources at urban sites (Faoro and McMullen, 1977).

specific current atmospheric cadmium levels explicitly associated with fossil fuel usage, it has been estimated that approximately 59 tons of cadmium are presently emitted yearly due to fossil fuel combustion, with approximately 7 tons of that being derived from coal-burning power plants. A matter of much growing concern is potential increased release of cadmium into the environment as a result of expected future increases in combustion of coal in power plants. Such increased utilization of coal is a key component in the United States effort to increase domestic energy independence. Workers at the Lawrence Livermore Laboratory have estimated that an additional one billion tons of coal may be consumed annually by 1990 (Berry and Wallace, 1974). This should be compared to the present consumption rate of 500 million tons annually (Bond et al., 1972). The expected corresponding emission of cadmium via this fuel utilization, according to EPA data (U.S. EPA, Sources of Atmospheric Cadmium, 1978), would be 16 tons annually by 1985 if emissions were controlled only at current levels. Much of this projected increase in cadmium emissions associated with expanded coal usage, however, is expected to be offset by expanded use of emission controls (U.S. EPA, Sources of Atmospheric Cadmium, 1978).

The foregoing estimates projecting that increased cadmium emissions arising both from municipal incinerators and coal-fired power plants will be largely offset by widespread use of emission control technology should be viewed with caution. According to Natusch et al. (1974) who studied emissions from eight coal-fired power plants: "Existing particle collection devices, although highly efficient for the removal of large particles and thus for the reduction of bulk emissions, preferentially allow the emission of the smallest, most toxic particles." Furthermore, "estimates of toxic

element emissions, based on analyses of undifferentiated fly ash collected on particle precipitators, grossly underestimate the actual emissions." This is of special concern in regard to cadmium because cadmium is found to be most concentrated among the smallest respirable particles emitted from coal fires and found in fly ash (Natusch et al., 1974). These small particles are those that can most easily pass through conventional control equipment and have the highest deposition in the respiratory tract. These particles, 1-2 μm in diameter, have 3 to 18 times more of the toxic metals than fly ash particles >40 μm in diameter. Cadmium has been found to be enriched in the soil around a coal-fire power plant and also enriched in plant materials growing in this soil. The soil cadmium content correlates with the wind pattern of the area as well as the metal content of the coal burnt in the plant (Klein and Russell, 1973). Thus, not only would increased cadmium emissions from expanded coal-burning in power plants have an impact on ambient air levels, but such emissions would also impact secondarily on ground water and soil levels of cadmium via dust fall from the air.

Putting the United States' air cadmium levels into a broader perspective, it has been reported (Friberg et al., 1974) that worldwide ambient air cadmium levels are generally less than 0.003 $\mu g/m^3$ (3 ng/m^3) in rural areas, but the yearly average may range as high as 0.050 $\mu g/m^3$ (50 ng/m^3) in industrialized urban areas. In contrast, at the extreme, weekly or monthly averages around 0.50 $\mu g/m^3$ (500 ng/m^3) have been recorded in the vicinity of cadmium-emitting industries (Friberg et al., 1974).

4.2.2 Drinking Water

The cadmium found in uncontaminated rural streams is derived from natural sources and generally contains less than 1 ppb or 1 μg/l of cadmium

(Friberg et al., 1971). In some cases, however, that naturally-derived cadmium is augmented by cadmium from industrial and commercial sources. Such contamination can occur, for example, as a result of: (1) mining and smelting operations; (2) other manufacturing processes utilizing mainly cadmium (as in electroplating operations) or closely associated metals such as zinc (as in the galvinizing of steel); or (3) industrial waste disposal (as in the disposal of spent solutions from plating processes). Cadmium contamination of water also occurs secondarily to the use of phosphate fertilizers and landspreading of sewage sludge on agricultural land or the leaching of cadmium from land fill or other disposal sites. It is often difficult to state with much precision the extent to which any of the above sources of cadmium may individually contribute to water cadmium levels in any given geographic region. Nevertheless, industrial and commercial processes are usually concentrated most heavily in urban areas; it is therefore not surprising that urban waterways tend to have considerably higher water concentrations of cadmium than do rural streams. Thus, while non-polluted rural and city water often contains less than 1 μg/l, cadmium levels have been found to increase to levels as high as 10 μg/l as a result of industrial discharge or use of metal or plastic pipes (Friberg et al., 1974).

Potable water supplies in the United States have been monitored for cadmium levels since 1969, when the Community Water Supply Survey was carried out on 969 water systems by the U.S. Public Health Service (USPHS, 1970). At that time only four out of 2595 distribution samples (Taylor, 1971) exceeded the USPHS drinking-water standard of 10 parts per billion (ppb) or 10 μg/l. The average drinking-water value was 3 ppb with a

maximum level of 0.11 parts per million (ppm). More recent data, through March, 1975, has been obtained by EPA (U.S. EPA, 1975); and none of the 594 analyses were above the 10 ppb standard. Particular attention in the recent survey was paid to water systems in which there is soft to "acid" water (pH 5 to 6) since cadmium and other metal dissolution from plumbing is more probable with this type of water. Two studies, done in Boston and Seattle by Deane et al. (1976) found no samples in the former locale exceeding the USPHS standard, while in Seattle 7.0 percent of the homes exceeded this value (10 ppb). Thus, in general, cadmium in drinking water does not now appear to contribute significantly to cadmium exposure for most Americans. There appears to exist, however, a need for more systematic studies to assess the extent of "pick up" of cadmium in water lines, determined by simultaneous studies of water supplies and tap water levels.

4.2.3 Soils

Soil levels of cadmium are important to man in terms of the terrestial food chain, starting with plants. Soil levels in turn reflect both geochemical and anthropogenic components. In regard to geochemical components, as suggested in Table 4-2, natural soil cadmium levels in remote areas are generally less than 0.1 ppm. Some regions, such as east-central Nevada and the Salinas Valley of California, however, have higher natural levels of soil cadmium due to higher natural content of native rocks, i.e., basaltic versus granite rocks (Fleischer et al., 1974). On the other hand, soil cadmium levels are often also greatly increased by industrial activities, as is also shown in Table 4-2.

Gowen et al. (1976) compiled urban and suburban cadmium-soil values for American cities and these tabulations appear in Table 4-3. It may be

Table 4.2. CADMIUM IN SOILS

Locality and type of soil	Number of samples	Depth (cm)	Cadmium content (ppm)	
			Range	Average
		Normal soils		
U.S.S.R., tundra, podsols, forest, red earth	40	A, B, and C horizons	0.01-0.07	0.06
Poland, distant from industrial areas	33	0-20	0.04 (max)	0.016
Wales, Ystwyth Valley				1.0
Maryland, Missouri, Ohio, 32 m from highways[a]	4	10-15	0.12-0.52	0.26
Helena Valley, Montana, 18-60 km from smelter	17	6-10	<0.5-2[b]	1.4[b]
Annaka City, Japan, 900 m from refinery	2	40-60	0.3-0.4	0.35
Southwest Wales	4		0.3-0.5	0.4
Lower Fraser Valley, British Columbia	33	Surface		0.88
		Contaminated soils		
Poland, industrial areas	67	0-20	0.3-0.8 (max)	0.17-0.28
Wales, Ystwyth Valley, contaminated			1.5-3.0	
Maryland, Missouri, Ohio, 8 m from highways[a]	4	0.5	0.90-1.82	1.28
Helena Valley, Montana, 1 km from smelter	7	0.10	26-160	72
Annaka City, Japan				
150-230 m from smelter		Surface	23-88	
900 m from smelter		5	44	
Poland, 600 m from zinc metallurgical factory	1	0-10	250	
	1	15-30	110	
Southwest Wales, Swansea, 1.5 km from contaminated area			26	
Bartlesville, Oklahoma, 1500 ft from smelter		12.5-27.5	450	
British Columbia, 15 m from smelter	4	Surface	7.9-95.2	49.0
Grand Rapids area, Michigan				
Residential area	70	0-5		0.41
Agricultural area	91	0-5		0.57
Industrial area	86	0-5		0.66
Airport	7	0-5		0.77

[a]Samples collected near U.S. 1, Beltsville, Maryland; Washington-Baltimore Parkway, Bladensburg, Maryland; Interstate 29, Platte City, Missouri; Seymour Road, Cincinnati, Ohio.

[b]These values probably reflect some contamination.

Source: Adapted from Fleischer et al., 1974, Table 6, p. 264. Data collected from several sources

Table 4-3. CONCENTRATIONS OF CADMIUM IN URBAN AND SUBURBAN SOILS--1972[a]

SMSA	Number of samples		Cadmium, ppm[b] Arithmetic mean	Geometric mean	Range	Percent of positive detections
Des Moines IA	59	Urban	0.89	0.640	0.1 - 3.56	100
	25	Suburban	0.28	0.124	0.00 - 1.76	80
Fitchburg MA	26	Urban	0.13	0.059	0.00 - 0.70	62
	10	Suburban	0.13	0.051	0.00 - 0.38	60
Lake Charles LA	16	Urban	0.36	0.015	0.00 - 5.32	25
	54	Suburban	0.01	0.002	0.00 - 0.11	7
Pittsburgh PA	51	Urban	1.21	0.743	0.00 - 4.95	98
	138	Suburban	0.90	0.454	0.00 - 8.03	93
Reading PA	10	Urban	0.63	0.261	0.00 - 1.70	90
	41	Suburban	0.25	0.039	0.00 - 2.45	44

[a]Source: Gowen et al., 1976.

[b]Sensitivity 0.5 ppm.

seen that urban areas almost invariably have higher cadmium amounts than suburban areas. Also, industrialized areas typically have higher levels than less industrialized regions; Fitchburg, MA, for example, had suburban and urban values of 0.13 ppm each in comparison to readings of 0.25 and 0.65 ppm for Reading, PA, and values of 0.91 and 1.21 ppm for Pittsburgh, PA. Consistent with this, in another study, Yost et al. (1975) found higher-than-normal (>0.4 ppm) levels of 2.5 or 14.0 ppm in samples obtained in East Chicago, Indiana.

Significant contamination of soil with cadmium also occurs in certain rural areas as a result of man's activities. For example, the study of Munshower (1972) found soil levels varying as a function of distance from a smelter in East Helena, Montana. The levels ranged from 27.3 ppm (0 to 5.0 cm in depth) at 2.4 km away to 1.5 ppm at 33.8 km away, illustrating well that cadmium particles in the air can settle to the ground and add measurably to soil cadmium levels.

Also, agricultural use of land adds to the soil-cadmium burden. In that regard, a significant contribution comes from phosphate fertilizers, with cadmium values varying from 0.15 ppm in untreated soils to 3.38 ppm in lands dressed with phosphate fertilizers. Another practice that could contribute significantly to soil cadmium levels in agricultural land, however, is the increasing use of landspreading of municipal sewage sludge and other cadmium-containing materials on commercial crop lands; and this is a matter of considerable concern for several regulatory agencies such as the EPA and FDA.

The reason for concern about increased spreading of sewage sludge on agricultural land is the fact that the cadmium content of such sludge has

been found to range from a few ppm to several thousand ppm; indiscriminate increased usage of sludge for fertilization of croplands could therefore result in a major new source of contamination of foodstuffs and significant increases in dietary cadmium exposure of the general population. The magnitude of the current and potential future sludge problem is illustrated by the data contained in Table 4-4.

Table 4-4 shows amounts of sewage sludge containing varying concentrations of cadmium that have been disposed of by certain United States cities, including by landspreading on agricultural land. The information listed in the table is based on data compiled by the EPA Office of Solid Waste Management in 1976 and reported in two separate sources, i.e., EPA Multimedia Levels Cadmium (1977) and Impact of Annual Cadmium Application Rates on Current Municipal Sludge Landspreading Practices (1978). The sludge production from the cities listed in Table 4-4 totals 3706 dry mt/day produced, and approximately 672 dry metric tons (mt) per day were reported as being agriculturally landspread, which represents about 25 percent of the sludge generated. It is important to note, while many municipalities produce sludge with relatively low cadmium content (less than 10-15 ppm), many other towns and cities produce sludges containing cadmium levels in excess of 100 ppm (100 mg/kg). Low cadmium content sludge, however, is not the only kind spread on agricultural land. Some sludges having cadmium contents in excess of 100 ppm have been used. For example, one town was reported as having landspread its daily production of 2 dry mt/day of sludge, with a cadmium content of 3171 ppm, on agricultural land. Also, from among the 41 "unknown" cities which produce sludges with cadmium concentrations of 1-970 ppm, ten cities were reported as

Table 4-4. AMOUNTS OF MUNICIPAL SEWAGE SLUDGE OF VARYING CADMIUM CONTENT ANNUALLY PRODUCED BY MAJOR U.S. CITIES AND DISPOSED OF BY VARIOUS METHODS*

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
New York, N.Y.						
(Metropolitan area)		6 - 163	228	Ocean	--	I.D.
Hampstead-Bay Park	1975	70			--	8
Long Beach	1975	18				8
Bowery Bay	1975	47				8
Coney Island	1975	8				"
Humts Point	1975	18				"
Jamaica	1975	4				"
Newton Creek	1975	71				"
Owls Head	1975	18				"
Port Richmaon	1975	3				"
Rockaway	1975	16				"
Tallmans Island	1975	6				"
26th Ward	1975	17				"
Wards Island	1975	6				"
Hampstead-West Long Beach	1975	4				"
Yonkers	1975	163				"
Chicago, Ill.	1976	10 - 210	518	Land application	182[b]	4
North Side	1976	180		Give away		"
Calumet	1976	42				"
Hanover Park	1976	10				"
Lemont	1976	16				"
W. Southwest	1976	210				I.D.
Los Angeles, Cal.		120	127	Ocean		I.D.
(City & County)		60	295	Sale for compost		"
Philadelphia, Pa.						
N.E. Plant	1976	90	168	Ocean		4
S.W. & S.E.	1976	25	14	Compost		"
Detroit, Mich.		290	145	Incineration		"

Table 4-4. (continued).

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Houston, Tex.	1972-73	112	91	Head dried for		6
North Side	1976	17		brokerage sale		9
Simms	1976	22				I.D.
Baltimore, Md.		25	112	Landfill		4
Back River		7				"
Patapsco		9				"
Dallas, Tex.	1976	59	32	Lagoon		9
Washington, D.C.	1975	22	330	Landfill,		3
			14	Compost		
Cleveland, Ohio						
Southerly		390	114	Landfill		4
Westerly		578				"
Indianapolis, Ind.						
Belmont		240	148	Incineration,		"
Southport		260		Land application		"
Milwaukee, Wis.	1972-73	444	82-171	Miloganite-soil	82	
Jones Island		107		conditioner		6
South Shore		50				4
San Francisco area	1975	15	45	Landfill,		2
			2	Land application		
Boston, MA	1973-75	82	78	Ocean		5
Denver, CO	1972-73	46	64	Land application	64	6
Seattle, WA	1972-73	64	33	Landfill, Soil conditioner		"
Atlanta, GA	1972-73	101	20	Landfill or soil conditioner		"

Table 4-4. (continued).

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Newark, NJ	1975	173	104	Incineration		8
Unknown		19	45	Agricultural land	45	I.D.
Miami, FLA	1972-73	149	15	Soil conditioner		6
Tampa, FLA	1975	10	9	Land application		7
Unknown		11	30	Agricultural land	30	I.D.
Little Ferry, NJ	1975	240	38	N.A.		8
Unknown		9	23	Agricultural land	23	I.D.
Unknown		13	23	Agricultural land	23	I.D.
Grand Rapids, MI	Prior to 1974	480	23	N.A.		1
Flint, MI	Prior to 1974	20	23	N.A.		1
Syracuse, NY	1972-73	200	22	Solvay process		6
Madison, WI		73	14	N.A.		4
Unknown		160	18		18	I.D.
Warren, MI	Prior to 1974	110	17	N.A.		1
Unknown		100	14	Agricultural land	14	I.D.
Unknown		5	14	Agricultural land	14	I.D.
Macon, GA	1976	6	15	Land application	15	10
Elizabeth, NJ	1975	72	25			8

Table 4-4. (continued).

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Camden, NJ		601	14	Ocean		4
Springfield, MO	1976	54	13	Land application	13	10
Saginaw, MI	Prior to 1974	48	11	N.A.		1
Pontiac, MI	Prior to 1974	12	9	N.A.		"
Kalamazoo, MI	Prior to 1974	12	9	N.A.		"
Ann Arbor, MI	Prior to 1974	4	9	N.A.		"
Unknown		10	9	Agricultural land	9	I.D.
Unknown		269	9	Agricultural land	9	I.D.
Anderson, IN	1972-74	170	9	Land application	9	11
Unknown		176	8	Agricultural land	8	I.D.
Unknown		17	8	Agricultural land	8	I.D.
Kokomo, IN	1972-74	806	7	Lagoon		"
Wyoming, MI		14	6	N.A.		1
Bay City, MI	Prior to 1974	80	6	N.A.		"
Jackson, MI	Prior to 1974	520	5	N.A.		"
Unknown		7	5	Agricultural land	5	I.D.
Danville, VA	1976	18	5	Agricultural land	5	10
Muskegon, MI	Prior to 1974	166	5	N.A.		1

Table 4-4. (continued).

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Linden, NJ	1975	65	10	N.A.		8
Battle Creek, MI	Prior to 1974	8	5	N.A.		1
Unknown		683	5	Agricultural land	5	I.D.
Unknown		95	5	Agricultural land	5	I.D.
Unknown		16	5	Agricultural land	5	I.D.
Port Huron, MI	Prior to 1974	8	4	N.A.		1
East Lansing, MI	Prior to 1974	6	4	N.A.		"
Unknown	Prior to 1974	4	4	Landfill and agric land	2	"
Ithaca, NY	1972-73	66	4	Soil conditioner		6
Easton, PA		16	4	Land application		I.D.
Midland, MI	Prior to 1974	10	4	N.A.		1
Unknown		61	4	Agricultural land	4	I.D.
Unknown		38	4	Agricultural land	4	I.D.
Unknown		11	4	Agricultural land	4	I.D.
Columbus, IN	1976	2	3	Land application	3	10
Holland, MI	Prior to 1974	10	3	N.A.	3	1
Ypsilanti, MI	Prior to 1974	166	3	N.A.		"
Sayreville, NJ	1975	39	61	N.A.		3

Table 4-4. (continued).

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Unknown		12	3	Agricultural land	3	I.D.
Hopkinville, IN	1976	18	3	Agricultural land	3	10
Xenia, OH	1976	80	3	Land application	3	10
Unknown		7	3	Agricultural land	3	I.D.
Monroe, MI	Prior to 1974	8	3	N.A.		1
Unknown		10	3	Agricultural land	3	I.D.
Marquette, MI	Prior to 1974	2	3	N.A.		1
Muskegon Heights, MI	Prior to 1974	150	3	N.A.		"
Mt. Clemons, MI	Prior to 1974	12	3	N.A.		"
Trenton, MI	Prior to 1974	8	3	N.A.		"
Sault Ste. Marie, MI	Prior to 1974	2	2	N.A.		"
Logansport, IN	1972-74	663	3	Land application		11
Traverse City, MI	Prior to 1974	10	2	N.A.		1
Adrian, MI	Prior to 1974	260	2	N.A.		"
Owosso, MI	Prior to 1974	1,100	2	N.A.		"
Mt. Pleasant, MI	Prior to 1974	14	2	N.A.		"
Benton Harbor, MI	Prior to 1974	220	2	N.A.		"
Escanaba, MI	Prior to 1974	10	2	N.A.		"

Table 4-4. (continued).

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Dixon, IL	1976	16	2	Land application	2	10
Frankfort, IN	1976	3,171	2	Land application	2	"
Las Virgenes CA	1976	5	2	Land application	2	"
Unknown		8	2	Agricultural land	2	I.D.
Peru, IN	1972-74	164	2	Land application		11
Crawfordsville, IN	1972-74	15	2	Land application		11
Unknown		168	2	Agricultural land	2	I.D.
Iron Mountain, MI	Prior to 1974	6	2	N.A.		1
Albion, MI	Prior to 1974	48	2	Agricultural land	2	"
Unknown		16	2	Agricultural land	2	I.D.
Unknown		9	2	Agricultural land	2	I.D.
Unknown		19	2	Agricultural land	2	I.D.
Niles, MI	Prior to 1974	14	2	N.A.		1
Grand Haven, MI	Prior to 1974	14	2	N.A.		"
Menominee, MI	Prior to 1974	4	1	N.A.		"
Cadillac, MI	Prior to 1974	36	1	N.A.		"
Lebanon, IN	1972-74	40	1	Agricultural land	1	11
Noblesville, IN	1972-74	12	1	Land application		"

Table 4-4. (continued).

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Marshall, MO	1976	16	1	Land application	1	10
Wilmington, OH	1976	15	1	Agricultural land	1	"
Unknown		7	1	Agricultural land	1	I.D.
Unknown		1	1	Agricultural land	1	I.D.
Charlotte, MI	Prior to 1974	14	1	N.A.		1
Ironwood, MI	Prior to 1974	4	1	N.A.		"
Hancock, MI	Prior to 1974	4	1	N.A.		"
Three Rivers MI	Prior to 1974	44	1	N.A.		"
Chippewa Falls, WI	1976	7	1	Land application	1	10
Litchfield, IL	1976	6	1	Land application	1	"
Kendallville, IN	1976	28	1	Land application	1	"
Unknown		22	1	Agricultural land	1	I.D.
Unknown		18	1	Agricultural land	1	I.D.
Unknown		970	1	Agricultural land	1	I.D.
Unknown		16	1	Agricultural land	1	I.D.
Marshall, MI	1976	16	1	N.A.		10
Gladstone, MI	Prior to 1974	4	1	N.A.		1
Howell, MI	Prior to 1974	18	1	N.A.		1

Table 4-4. (continued).

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
Manistique, MI	Prior to 1974	4	1	N.A.		"
Tipton, IN	1972-74	11	1	Land application		11
Unknown		10	0.5	Agricultural land	0.5	I.D.
Unknown		9	0.5	Agricultural land	0.5	I.D.
Milford, MI	Prior to 1974	2	0.5	N.A.		1
Essexville, MI	Prior to 1974	4	0.5	N.A.		"
Norway, MI	Prior to 1974	2	0.5	N.A.		"
St. Ignance, MI	Prior to 1974	4	0.5	N.A.		"
Unknown		7	0.5	Agricultural land	0.5	I.D.
Unknown		23	0.5	Agricultural land	0.5	I.D.
Unknown		8	0.5	Agricultural land	0.5	I.D.
Constantine, MI	Prior to 1974	16	0.5	N.A.		1
Dexter, MI	Prior to 1974	36	0.5	N.A.		"
Lanse, MI	Prior to 1974	8	15	N.A.		"
Unknown		13	0.3	Agricultural land	0.3	I.D.

Table 4-4. (continued).

CITY	YEAR	SLUDGE CADMIUM, (ppm)	QUANTITY (SLUDGE)	PRESENT DISPOSITION	TOTAL LANDSPREAD	SOURCE OF INFORMATION[a]
TOTAL Named Cities (N = 61)	2 - 3,171	2 - 3,171	3,423		391	
TOTAL Unknown Cities (N = 40)	1 - 970	1 - 970	283		281	
TOTAL CITIES (N = 101)	1 - 371	1 - 371	3,706 3,706 = 30% of sludge generated in U.S.		672 672 = 25% of sludge agriculturally landspread	

[a]Sources of Information:

1. Blakeslee, Paul A. 1973. "Monitoring Considerations for Municipal Wastewater Effluent and Sludge Application to the Land," Recycling Municipal Sludges and Effluents Joint Conference, Champaigne II.
2. Brown and Caldwell. 1975. San Francisco Bay Area Municipal Wastewater Solids Management Study (May 1975).
3. Camp, Dresser, and McKee. 1975. Alternative Sludge Disposal Systems for the District of Columbia Water Pollution Control Plant at Blue Plains (December 1975).
4. Ehorn, Douglas. Personal communication. EPA-Region V; and Albert Montague, EPA-Region III. 1976.
5. EPA, Region I Office, Solid Waste Staff communication. 1976.
6. Furr, A.K., et al. 1976. Mutielement and Chlorinated Hydrocarbon Analysis of Municipal Sewage Sludges of American Cities. Journal of Environmental Quality (July 1976).
7. Greeley and Hansen. 1975. Report on Management and Disposition of By-Product Solids Hookers Point Sewage Treatment Plant, City of Tampa, Florida (June 1975).
8. Interstate Sanitation Commission. 1975. Phase One Report of Technical Alternatives to Ocean Disposal of Sludge in New York City. By Camp, Dresser, and McKee for New Jersey Metropolitan Area (1975).
9. Public Works Directors. (N.D.) Personal Communication.
10. SCS Engineers. 1976. Environmental Assessment of Municipal Wastewater Treatment Sludge Utilization Practices. EPA Contract NO. 68-01-3265. Work ongoing.
11. Sommers, L. E., D. W. Nelson, and K. J. Yost. 1976. Variable Nature of Chemical Composition of Sewage Sludges. Journal of Environmental Quality. 5(3).

I.D.: Impact of Annual Cadmium Application Rates on Current Municipal Sludge Landspreading Practices, EPA, 1978.

[b]Chicago is planning to landspread by opting for the "crop monitoring" approach allowed under proposed sludge criteria (Federa Register, Monday, February 6, 1978, Part II, Vol 43, No. 25; Pg. 4954 - 4955).

producing 70 dry mt/day of sludge with cadmium content above 25 ppm that was agriculturally landspread. Other data discussed below under "Food" as a source of cadmium exposure provides a perspective on the implications of agricultural spreading of sewage sludge with varying cadmium concentrations, and phosphate fertilizers as well, for consequently increased soil and crop cadmium content.

4.2.4 Food

Cadmium contamination in air, water, and soil not only affects man directly through contact with those media, but also through the infiltration of the metal from those sources into man's food chain. No effort will be made here to trace in detail cadmium's transport via the food chain to man. It should be noted, however, that man depends on five major categories of food sources: (1) land plants, (2) land animals and animal products, (3) freshwater fish, (4) marine fish and free-moving crustaceans, and (5) shell fish.

Incorporation of cadmium into the above dietary food elements appears to occur through a variety of mechanisms, with several sometimes operating simultaneously. From among such mechanisms listed by EPA's recent assessment (Multimedia Levels Cadmium, 1977), the following appear to be of most importance:

(1) Uptake from soils by roots of food plants. This may occur:

a. Naturally where cadmium is a normal constituent of soils.

b. As an impurity (cadmium oxide) in phosphate-treated soils, especially with "superphosphate" fertilizer use.

c. In soils fertilized by sewage sludge containing cadmium.

d. By soil contamination from runoff of mine tailings or from electroplating washing process.

(2) Meat animals may accumulate cadmium in liver and kidney from feed crops that take up the metal from contaminated and naturally high-cadmium content soil.

(3) Mollusks and crustaceans normally concentrate cadmium from ambient waters, as do most other aquatic organisms.

Oral ingestion of food probably represents the single most important source of cadmium in man, especially in non-smokers. It may, in part, also represent a secondary exposure from airborne cadmium to the extent that airborne cadmium probably contributes some amount of the metal to food via deposition in water and on land from which food crops and animals are obtained. No thorough analysis of the contribution of airborne cadmium to food will be attempted here, but it should be kept in mind in considering the information that follows. Another issue not addressed in detail here, but important for putting the present discussion into perspective, is that of how much of the cadmium eventually showing up in food is derived from naturally occurring sources and how much accumulates secondarily from man's industrial and waste-disposal activities.

In EPA's recent analysis (Multimedia Levels Cadmium, 1977) it was noted that foods average about 0.05 ppm cadmium (wet weight), but there is wide variation across different food items, with maximum concentrations depending on the source from which they were obtained. The amounts found in different food categories in the U.S.A. in the late 1960's were reported by the United States Food and Drug Administration (FDA) to be as indicated in Table 4-5, as estimated from several studies (Corneliussen, 1970;

Table 4-5. CADMIUM CONTENT IN DIFFERENT FOOD CATEGORIES IN THE U. S. A.[a,b]

Type of food	Cadmium, μg/g wet weight			
	1968-1969		1969-1970	
	No. >0.01	Maximum	No. >0.01	Maximum
Dairy products	10	0.09	9	0.01
Meat, fish, and poultry	21	0.06	22	0.03
Grain and cereal products	27	0.08	27	0.06
Leafy vegetables	27	0.08	28	0.14
Legume vegetables	16	0.03	10	0.04
Root vegetables	24	0.08	27	0.08
Garden fruits	25	0.07	27	0.07
Fruits	15	0.04	10	0.07
Oils, fats, and shortening	27	0.13	28	0.04
Sugar and adjuncts	18	0.07	9	0.04
Beverages	8	0.04	9	0.04
Potatoes	--	--	29	0.08

[a]Source: Corneliussen, 1970; Duggan and Corneliussen, 1972.

[b]Cadmium was analyzed by atomic absorption and/or polarography at a sensitivity of 9.01 μg/g.

Duggan and Corneliusson, 1972). Concentrations of cadmium found more recently by FDA in adult foods are seen in Table 4-6 (U.S. Dept. of Health, Education and Welfare, 1975). Adult foods consistently found in the surveys to have high levels of cadmium are: beef liver, hamburger, leafy vegetables, root vegetables, potatoes, grains and cereal products, and refined sugar products. Relatively high standard deviations for virtually all foods listed in Table 4-6, however, also suggest that quite high concentrations can be found in some samples of nearly every food type.

Estimates by the FDA of the contribution of different foodstuffs to daily adult dietary intake are shown in Tables 4-7 and 4-8, and the percentages of total daily cadmium intake estimated to be obtained via ingestion of different food groups are illustrated in Figure 4-3. As seen there, most of the food groups listed above as high in cadmium constitute major portions of the typical adult diet and contribute the largest percentages of daily dietary cadmium intake.

A matter of considerable interest is the estimation of daily dietary intake for Americans. Noteworthy in that regard are results from Total Diet Studies (market basket) surveys conducted by the FDA over a seven year period (1968-1974). As shown in Tables 4-7 and 4-8, cadmium intake from all food groups varied somewhat from year to year (totaling 36 and 51 μg/day for the two years shown in the tables for the "typical" teenage American male). The average of the median levels obtained over the seven year survey period was 33 μg/day, while the seven-year average of the means was 72 μg (U.S. Dept. of Health, Education and Welfare, 1975). This suggests that most individuals have intake levels below 30 to 50 μg/day, but some may have intakes substantially above 70 μg/day.

Table 4-6. CADMIUM CONTENT OF SELECTED ADULT FOODS[a]

Commodity	No. of samples	Average, ppm	Standard Deviation, ppm
Carrots, roots fresh	69	0.051	0.077
Lettuce, raw crisp head	69	0.062	0.124
Potatoes, raw white	71	0.057	0.139
Butter	71	0.032	0.071
Margarine	71	0.027	0.048
Eggs, whole fresh	71	0.067	0.072
Chicken fryer, raw whole or whole cut up	71	0.039	0.088
Bacon, cured raw, sliced	71	0.040	0.160
Frankfurters	69	0.042	0.111
Liver, raw beef	71	0.183	0.228
Hamburger, raw ground beef	71	0.075	0.122
Roast, chuck beef	71	0.035	0.034
Wheat flour, white	71	0.064	0.150
Sugar refined, beet or cane	71	0.100	0.709
Bread, white	70	0.036	0.063
Orange juice, canned frozen concentrate	71	0.029	0.095
Green beans, canned	71	0.018	0.072
Beans, canned with pork and tomato sauce	71	0.009	0.000
Peas, canned	71	0.042	0.113
Tomatoes, canned	71	0.042	0.113
Diluted fruit drinks, canned	71	0.017	0.052
Peaches, canned	71	0.036	0.061
Pineapple, canned	71	0.059	0.153
Applesauce, canned	71	0.020	0.027

[a]Source: U.S. Department of Health, Education, and Welfare, 1975.

Table 4-7. FOOD GROUPS BY MEAN CADMIUM CONTENT AND THEIR CONTRIBUTION TO DAILY CADMIUM INTAKE[a]

Food group	Concentration, ppm Mean	Cadmium intake μg/day	Percent of total daily diet	Contribution to daily cadmium intake, %
Leafy vegetables	0.051	3.18	2.0	6.2
Potatoes	0.046	9.11	7.0	17.8
Fruits	0.042	9.38	7.4	18.3
Grains and cereals	0.028	11.66	12.6	22.8
Oils, fats, and shortening	0.027	1.36	1.8	2.7
Root vegetables	0.021	0.76	1.2	1.5
Garden fruits	0.019	1.71	3.0	3.4
Meats, fish, and poultry	0.0093	2.49	9.9	4.9
Sugars and adjuncts	0.0083	0.68	2.8	1.3
Legume vegetables	0.006	0.42	2.5	0.8
Beverages	0.0057	6.49	23.9[b]	12.7
Dairy	0.005	3.94	25.9	7.7

[a]Source: Mahaffey et al., 1975.

[b]Includes water.

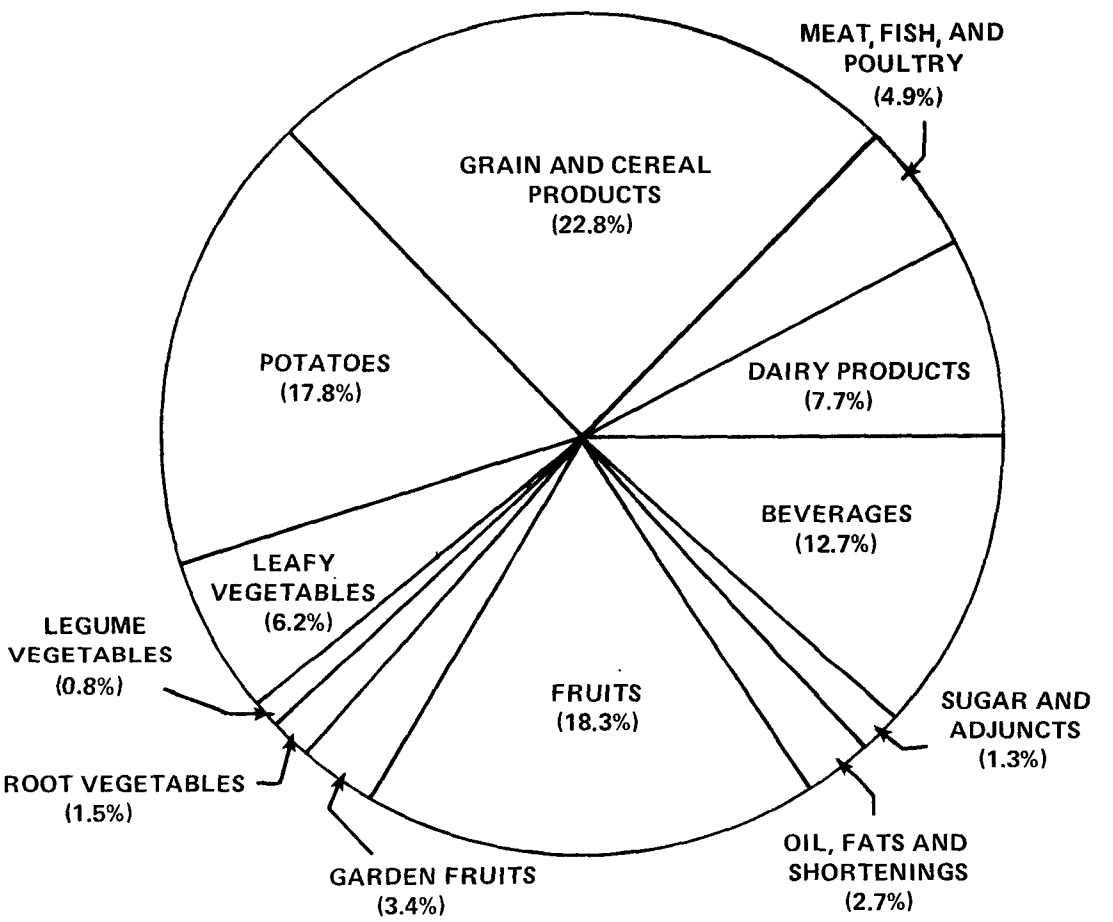


Figure 4-3. Contribution of food groups to cadmium intake.

From: Shibko and Braude (1978)

Table 4-8. CADMIUM INTAKE OF TEEN-AGE MALES BY FOOD CLASS[a]

Food class	Average consumed g/d	Cadmium* residue ppb	Cadmium intake µg/d
Dairy products	704	5.7	4.0
Meat, fish, poultry	262	15.3	4.0
Grain and cereal products	424	23.3	9.9
Potatoes	177	48.0	8.5
Leafy vegetables	54	40.5	2.2
Legume vegetables	66	6.3	0.4
Root vegetables	32	32.3	1.0
Garden fruits	88	14.7	1.3
Fruits	222	3.0	0.7
Oils, fats, shortening	72	15.3	1.1
Sugars and adjuncts	83	10.0	0.8
Beverages (including water)	684	3.0	2.1
Total	2868		36

*Trace values assumed as 10 ppb.

[a]From U.S. Dept. of Health, Education and Welfare. "Compliance Program Evaluation, FY '74 Total Diet Studies (7320.08)". Food and Drug Adm., Bureau of Foods, 1975.

Also of interest in regard to the issue of daily cadmium intake in the diet of the U.S. population are the results of a recent collaborative study, which was carried out jointly in the United States, Sweden and Japan (Kjellström, 1978) and included measurement of daily fecal cadmium excretion for human volunteers in each country. Based on observed fecal cadmium values, which may better reflect actual dietary cadmium intake than the above "market basket" surveys, adult dietary intake of cadmium in the U.S. population was reported to average approximately 18 μg/day for non-smokers. This arithmetic mean intake, however, was associated with a relatively large standard deviation of ± 8 μg, indicating that diets vary considerably among members of the U. S. population in terms of cadmium content. In fact, based on the observed distribution, the intake of a significant number of individuals (over 2.5 percent) exceeds 32 μg/day and for some reaches or exceeds 40 to 50 μg/day. It thusly appears that an average daily dietary cadmium intake for Americans can reasonably be estimated to be within the range of 10 to 50 μg/day; however, it is also clear that significant numbers of individuals exceed 50 μg/day level of intake, as indicated by both the "market basket" survey results reported by FDA and the "fecal excretion" studies discussed here.

While the above estimates are among the best available for current levels of daily dietary cadmium intake, they may not be accurate indicators of future American dietary exposure to cadmium. Rather, increased amounts of dietary cadmium can be expected to be ingested in the future if use of high cadmium-containing phosphate fertilizers on U.S. crop lands is expanded and as a consequence of uncontrolled landspreading of cadmium-contaminated sewage sludge on agricultural land.

Several studies provide important information on the likely impact of cadmium loading of agricultural land on soil and crop cadmium contents. For example, at a 1 kg/ha cadmium application rate, Dowdy and Larson (1975) found that lettuce cadmium increased five-fold compared to control levels, while carrots, radishes, and potatoes showed a two-fold cadmium increase and sweet corn leaves and grain increased from 0.26 to 1.32 ppm cadmium and from 0.02 to 0.05 ppm cadmium, respectively. In a similar study, Clapp et al. (1976) showed that, at a 5.1 kg/ha cadmium loading rate on sandy soil in Minnesota, the cadmium content of field corn leaves normally fed to livestock increased five-fold, but the corn grain levels were not changed.

Maclean (1976) applied 0, 2.5, and 5.0 ppm cadmium (approximately 0, 5.5, and 11 kg Cd/ha) to Grenville loam soil with a neutral pH of 7.1 and observed the effect on cadmium uptake by several vegetables and field crops. The results obtained are shown in Table 4-9 and indicate that many vegetables and root crops increased their cadmium uptake by five-fold at the 5.5 kg/ha cadmium application rate. At the same application rate, oats and soybeans, as intermediate cadmium accumulators, increased their cadmium content by six-fold, while tobacco and lettuce, as high cadmium accumulators like Swiss chard, had more than 10-fold increases in cadmium.

When soil pH is taken into account, then even more striking effects of cadmium loading on crop uptake of the metal are seen. Specifically, the uptake of cadmium by many plants is dramatically increased by acidic soils, as illustrated in Figure 4-4 for Swiss chard. The practical consequences of this for impications of sewage-sludge landspreading on agricultural land are well demonstrated by the data in Table 4-10 showing the results of studies on field sites that received sewage-sludge treatment for several

Table 4-9. CADMIUM CONTENT OF SEVERAL CROPS AND TISSUES AS A FUNCTION OF CADMIUM LOADING OF SOIL[a]

Crop	Tissue	Cd Content of Crop Tissue, ppm		
		Added Soil Cd, ppm		
		0	2.5	5.0
Timothy	Tops	0.21	1.04	1.41
Alfalfa	Tops	0.28	1.34	1.72
Corn	Tops	0.22	1.84	2.68
Oat	Straw	0.29	2.30	3.70
Oat	Grain	0.21	1.50	2.07
Soybean	Veg.	0.71	3.95	4.88
Soybean	Grain	0.29	1.88	2.51
Tomato	Veg.	0.51	5.26	6.46
Tomato	Fruit	0.23	0.99	1.03
Potato	Tops	0.58	3.46	7.35
Potato	Tubers	0.18	0.89	1.09
Carrot	Tops	0.46	5.66	7.70
Carrot	Roots	0.24	2.53	2.65
Lettuce	Tops	0.66	7.72	10.36
Tobacco	Tops	0.49	5.41	11.57

[a](From Maclean, 1976) Grenville loam pH = 7.1

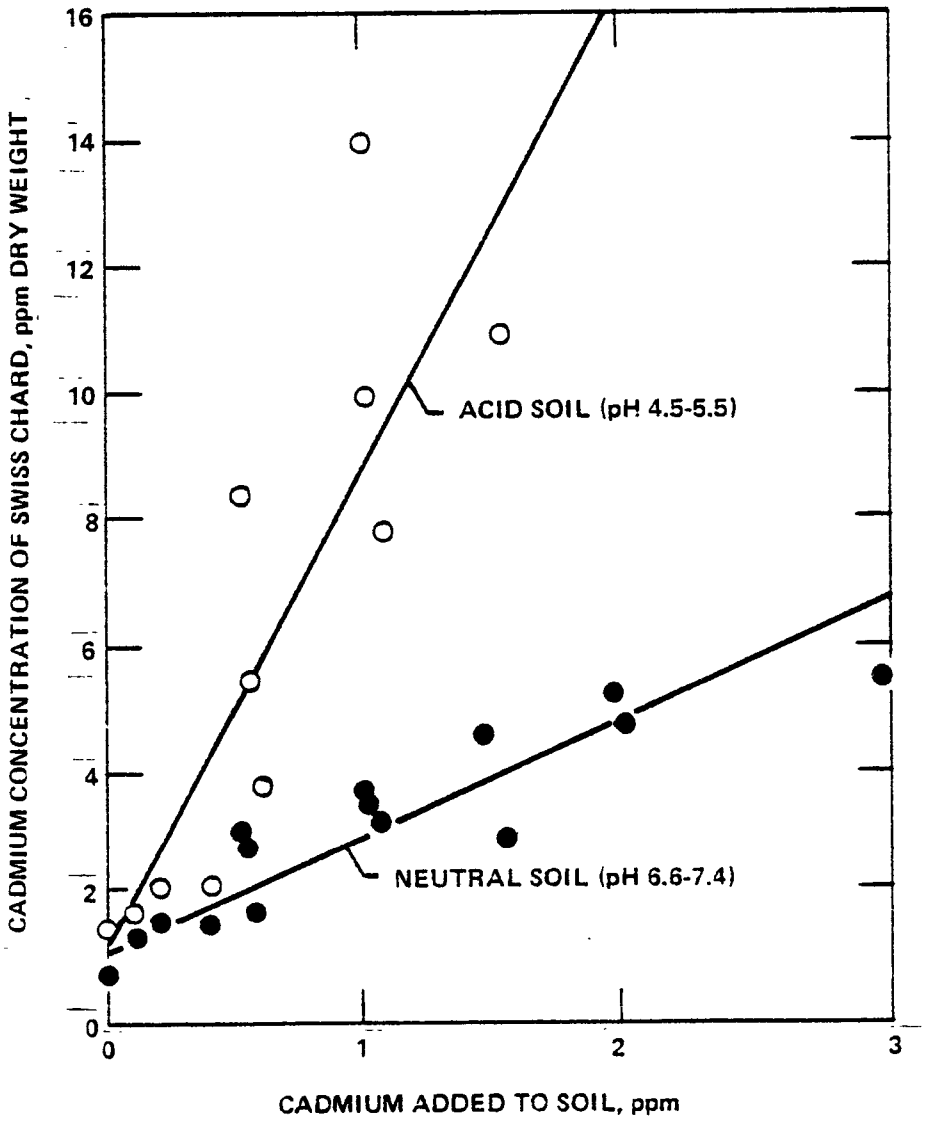


Figure 4-4. Effects of soil pH on cadmium uptake by vegetables.

From: Lucas, Pahren, Ryan and Dotson (1978)

Table 4-10. Cd CONTENT OF SOILS AND CROPS GROWN ON ACID AND LIMED SLUDGED SITES[a]

City	Sludged	Limed	Soil pH	Soil Total	Soil DTPA	Lettuce leaf	Swiss Chard D.	Swiss Chard W.D.	Soybean Leaf	Soybean Grain	Oat Boot	Oat Fodder	Oat Grain	Orchardgrass 1st	Orchardgrass 2nd
				-------Soil------		--ppm--	----ppm----		----ppm----		--------ppm--------			----ppm-----	
1	1967-75	No	5.08	3.30	2.07	17.53	28.03	23.18	2.05	0.48	----	----	----	----	----
	1967-75	Yes	6.15	3.42	1.98	7.52	14.03	10.43	1.02	0.37	----	----	----	----	----
	No	No	5.75	0.15	0.06	1.07	0.58	0.64	0.24	0.20	----	----	----	----	----
	No	Yes	6.54	0.14	0.06	0.45	0.34	----	0.18	0.13	----	----	----	----	----
4	1962-75	No	5.36	1.06	0.64	4.00	2.29	**	0.89	**	0.37	0.59	0.23	0.41	0.56
	1962-75	Yes	6.22	0.97	0.52	1.36	0.89	**	0.43	**	0.18	0.19	0.07	0.21	0.26
	No	No	5.91	0.20	0.10	0.84	0.45	**	0.11	**	0.11	0.12	0.05	0.30	0.57
	No	Yes	6.64	0.20	0.07	0.71	0.15	**	0.10	**	0.11	0.09	0.04	0.17	0.17
9	1961-73	No	4.92	2.75	1.29	20.41	37.09	**	4.93	1.07	2.42	5.03	2.12	1.63	1.67
	1961-73	Yes	6.26	2.88	1.22	4.64	2.90	**	0.68	0.38	0.40	0.79	0.38	0.56	0.66
	No	No	4.93	0.30	0.15	1.61	**	**	0.44	0.20	0.25	0.50	0.22	0.56	0.34
	No	Yes	6.31	0.18	0.09	0.63	0.78	**	0.17	0.08	0.11	0.12	0.04	0.24	0.17
13	1967-74	No	5.70	9.58	6.30	49.86	46.16	22.96	5.93	1.50	6.55	10.94	3.38	2.31	3.69
	1967-74	Yes	6.37	6.79	3.70	9.91	11.02	5.94	0.90	0.68	0.61	0.86	0.54	0.70	1.17
	No	No	5.22	0.14	0.09	1.47	1.30	0.96	0.34	**	0.11	0.10	0.11	0.12	0.17
	No	Yes	6.21	0.13	0.07	0.58	0.41	0.45	0.25	0.11	0.10	0.06	0.07	0.06	0.16

[a]Source:

** = No sample due to animal damage

---- = Crop not grown

years. The actual annual loadings on a kg Cd/ha basis are not known, but the sludge cadmium content from cities 1, 4, 9, and 13 were 100, 22, 169, and 683 ppm, respectively. Sites for cities 1 and 4 had not received sludge since 1975 and for 9 and 13 not since 1973 and 1974, respectively, with the data in Table 4-10 being for crops grown in 1976. Not only do the results illustrate the importance of soil pH in determining crop uptake of cadmium, but they also show that cadmium persists in the soil in a form available for crop uptake even after cessation of sludge spreading. Thus, where uncontrolled spreading of high cadmium-containing wastes (such as sewage sludge) on agricultural land occurs, increased dietary ingestion of cadmium could result from increased cadmium uptake by food crops grown on those soils in years to come.

Phosphate fertilizers also contain appreciable levels of cadmium as a contaminant, and their widespread use on agricultural land can constitute a significant source of cadmium available for uptake by a variety of plants beyond the naturally occurring trace amounts of the element present in most soils. Levels of cadmium in phosphate fertilizers used in the United States domestic consumption can vary considerably from 9 mg/kg (9 ppm) for Florida phosphate ore to Western ore levels of 130 mg/kg (130 ppm) (EPA, 1974).

Schroeder and Balassa (1963) first suggested that cadmium contamination of soils from this source might lead to increased uptake of cadmium into the food chain. A number of other studies have appeared subsequently and have shown that cadmium uptake from fertilizer into plants is related to a number of factors such as the amount of phosphate applied, soil type, soil pH, types of plants grown, and parts of plants intended for foodchain use

(Williams and David, 1973, 1976; Lee and Keeney, 1975; Miller et al., 1976; Andersson, 1976; Reuss et al., 1976).

As expected, soil pH is important in the relative uptake of cadmium from phosphate treated soils into plants, with increasing pH leading to reduced cadmium uptake. Soil type as measured by cation exchange capacity (CEC) appears to be another important factor in transfer of cadmium from phosphate fertilizer into vegetation grown on it (Miller et al., 1976). The relative uptake of cadmium by plants also varies considerably with the type of plant grown on phosphate-dressed soils, leafy vegetables and grains showing relatively greater uptake than forage crops (Williams and David, 1973 and 1976; Reuss et al., 1978). Andersson (1976), in his studies of plant-available cadmium in soils, however, has found that soil levels of cadmium are not likely to be affected if the cadmium content of phosphate fertilizers is maintained below 8 ppm (mg/kg).

Since phosphate fertilizers and sewage sludge both add to the cadmium burdens of agricultural land, it would be of interest to consider the relative quantitative impact of the future intended use of sewage sludge with current use of phosphate fertilizers.

In Sweden, where sewage sludge use is limited and is regulated at a maximum permissable level of 15 ppm, the total amount of cadmium in sludge for 1973 was calculated to be 1260 kg cadmium (Stenstrom and Vahter, 1974), as compared to a corresponding cadmium total of ca. 10,000 kg cadmium in phosphate fertilizers.

In the United States, it is much more difficult to compare the relative impact of these two sources with respect to increasing the soil burden of agricultural lands. For one thing, it is to be expected that sewage sludge

use will increase in the future. While the relative growth in phosphate fertilizer use will probably be less, phosphate fertilizer consumption is widespread and without the extensive use of controls that will presumably apply to sewage sludge use (Solid Waste Disposal Facilities: Proposed Classification Criteria - EPA, 1978).

In this regard, Lee and Keeney (1975) have calculated that in Wisconsin cadmium added to agricultural land amounts annually to about 2150 kg/year. They also estimate that the potential contribution of cadmium from waste-water sludges would be ca. 1700 kg/year if all the sludge produced in Wisconsin were spread on the land. This total volume was estimated to contain a median cadmium concentration of 18 ppm (dry weight) in waste originating from 35 municipalities that serve 75 percent of the sewered population. On a total basis, it would appear that phosphate fertilizers are a more significant source of cadmium than sewage sludge in one particular state in the U.S. However, these authors argue that on a concentration basis, sludge may have the potential for increasing soil concentrations (mg Cd/kg soil) more significantly because of the much higher rates of application used. They calculate that, in Wisconsin, 186 years of phosphate fertilizer application would be required to equal a single 9 metric ton/hectare sewage sludge addition (at an 18 ppm median cadmium concentration level in the sludge).

There are certain factors which must be kept in mind regarding phosphate fertilizer as a source of cadmium: (1) the cadmium content of the phosphate as a function of the source of the phosphate and (2) the relative absence of any controls on the use of phosphate when compared to the developing picture of regulation for landspreading of sewage sludge.

Thus, any change in the sources of phosphate fertilizers with respect to domestic consumption may alter the total amounts of cadmium introduced onto agricultural land. Furthermore, the relative lack of any controls on the use of phosphate fertilizer with respect to increasing the cadmium levels of crops and other components of the foodchain, i.e., soil pH, types of soil, and types of plants, suggest that cadmium concentration in the food chain from this source is likely to continue.

It should be noted that much of the emphasis here on the effects of addition of materials to agricultural soils that raise soil cadmium levels is based on an awareness of the extreme difficulty in removing this added cadmium burden once in place. For example, the Japanese have had little success in restoring cadmium-contaminated crop land to its former productive use despite very extreme attempts at chemical debreedment of the cadmium in the soil (Friberg et al., 1974).

4.2.5 Other Sources

Cigarette smoking represents another major source of cadmium intake for many Americans. In fact, cadmium from cigarettes represents a substantial additional burden for smokers beyond that derived from food and other sources, putting smokers at special risk as discussed later. Amounts of respiratory intake from cigarettes range from 4 to 6 μg from two packs smoked per day. Amounts obtained from lesser use of cigarettes are shown in Table 4-11 along with a summary of contributions from other media to normal retention of cadmium, as reported by EPA (Multimedia Levels Cadmium, 1977). It should be noted that cadmium levels in cigarettes would be expected to increase greatly in the event of cadmium-containing fertilizers or sewage sludge being spread on tobacco fields, in view of tobacco being

Table 4-11. MEDIA CONTRIBUTIONS TO NORMAL RETENTION OF CADMIUM[a]

Medium	Adult	Exposure level	Daily retention (μg)
Ambient air	x 20 m^3/d	0.03 μg/m^3	0.15
Water	x 1 liter/d	1 ppb	0.09
Cigarettes Packs/day		μg/day[b]	
1/2		1.1	0.70[c]
1		2.2	1.41[c]
2		4.4	2.82[c]
3		6.6	4.22[c]
Food	x 2 kg/d	50 μg/day	3.0

[a]Source: Deane et al., 1976.

[b]Based on 0.11 μg per cigarette.

[c]Assumes a 64 percent retention rate.

one of the most avid accumulators of cadmium among crop plants. Prohibition of spreading high-cadmium content sludge on tobacco crop land, however, is expected to occur as part of future EPA regulatory actions (Solid Waste Disposal Facilities: Proposed Classification Criteria-EPA, 1978).

4.3 HEALTH EFFECTS SUMMARY

A wide variety of biological and adverse health effects of cadmium were described in earlier sections of this report, and the evidence for them from animal experiments and human epidemiologic studies was evaluated. At this point in discussing risk assessment it would be useful to summarize the more important health effects that appear to be of most concern in cadmium exposure.

Acute effects of cadmium on the lungs are of most immediate concern in cases of exposure to high levels of the metal via inhalation. Lethal levels of cadmium depend in part on particle size, form of metal compound encountered, and other factors. Estimates of LD_{50} exposure levels in rats and mice fall around 25 mg/m^3 for 30 min for particle size of 0.2 μ; and, for man, total pulmonary retention of 4 mg of cadmium after acute inhalation exposure is often fatal. Quite serious adverse effects, e.g., the induction of pneumonitis, are found at inhalation exposure levels far below lethal doses; significant lung impairment in man, for example, has been noted at cadmium-oxide fume levels below 1.0 mg/m^3.

In situations involving long-term cadmium exposure, especially at low to moderate levels, cadmium effects on the kidney appear to be among the most crucial ones, with renal damage currently widely accepted as the "critical effect" in terms of assessment of requisite exposure levels for induction of toxic actions of the metal. In fact, proteinuria resulting

from renal tubular damage is often utilized as a diagnostic sign indicative of likely cadmium intoxication. Estimations of amounts of cadmium accumulation in the kidney necessary for the induction of damaging effects resulting in proteinuria are important for efforts to calculate external exposure levels from various sources necessary to induce the "critical effect" of renal damage. Presumably, limiting exposures to levels assuring protection against renal damage by cadmium would, in essence, provide protection against any other significant adverse effects as well. This issue is discussed further in the present chapter under consideration of dose-effect dose-response relationships.

As stated in the discussion above, renal tubular dysfunction is the critical effect associated with chronic exposure to cadmium and is also that effect most relevant for populations at large. Two aspects of cadmium-induced renal dysfunction which are of paramount significance in any health risk assessment of cadmium can be framed as questions: 1) Is tubular proteinuria reversible or irreversible in nature, and 2) regardless of reversibility or irreversibility, is the presence of tubular proteinuria to be taken as a significant health effect?

In regard to the first issue, Piscator (1977) has reported data on eighteen cadmium workers that conclusively demonstrate the persistence of tubular proteinuria ca. twenty years after cessation of exposure. What is even more notable is the fact that irreversibility exists even at relatively low initial excretions of protein. Also, Kazantzis (1977) has reported on his study of six cadmium workers first surveyed in 1961, with five subjects surviving for the total survey period of 15 years. All of these workers were presumably exposure free or were in reduced

exposure settings after the first survey. All members of this study group displayed persistent tubular proteinuria at the second time point in the survey. Thus, available data clearly indicate that, for at least some individuals, cadmium-induced renal proteinuria can be irreversible.

As to the issue of renal tubular proteinuria being a significant health effect, the available evidence strongly indicates that it is indeed a significant health effect. Here, one can consider both the fact that tubular dysfunction, i.e., a systemic functional lesion, is itself a demonstrable impairment of the proper functioning of an organ; and, also, perhaps more importantly, the onset of tubular proteinuria signals the precarious status of an organ that has a substantially reduced reserve capacity for accommodating any additional stress and is functionally on the way to further, more involved dysfunction. Also, based on the fact that cadmium accumulation in the kidney occurs over many years and such accumulation does not markedly decay at the onset of tubular dysfunction, it is logical that tubular dysfunction would not be a transitory event since the lesioning agent, cadmium, remains at the target site to persist in imparting damage; nor would this early dysfunction necessarily be the sole extent of renal injury.

The data of Kazantzis (1977) supports the premise that a kidney already manifesting tubular proteinuria is at high risk for further functional complications. Of the six subjects in the survey noted above, one person developed ostiomalacia and a second suffered from chronic renal stone problems. All subjects showed persisting hypercalcuria and hypophosphaturia; of five subjects studied for uric acid clearance, all of them showed abnormally high clearance. Furthermore, four subjects had aminoaciduria,

and five individuals had glycosuria. Of these numbers in each category, uric acid clearance became elevated in three cases after the first survey; three cases of glycosuria, two cases of aminoaciduria, one case of hypercalcuria and one case of hypophosphaturia similarly developed subsequent to the first survey.

The reader is directed to a discussion of the above issues by clinical workers in the area of cadmium health effects, as reported in the Proceedings of the First International Conference on Cadmium, San Francisco, 1977, pp. 243-250.

While the above conceptualization of renal damage being the "critical effect" associated with cadmium toxicity has much evidence to support it, it should be noted that certain other evidence from animal studies now beginning to emerge hints at still other effects possibly occurring as early signs of cadmium intoxication. This may include, for example, certain "subtle" hormone effects that likely underlie reductions in plasma testosterone concentrations seen at cadmium exposure levels too low to produce signs of renal damage or any severe testicular necrosis. Other effects that may possibly occur at cadmium exposure levels below those producing renal damage include: (1) effects on reproduction and development, e.g., reductions in birthweights seen after oral exposure of pregnant animals and having some parallels in reports in the human epidemiology literature; (2) immunosuppression effects demonstrated to occur in animals at low oral exposure levels, but not yet confirmed in humans; and (3) certain mutagenic and carcinogenic effects observed in animal experiments or human epidemiology studies and for which "no-effect" dose levels have yet to be established. In regard to the latter types of effects, however,

it should be noted that several other working groups assessing the health effects of cadmium, in addition to the present authors, have concluded that only presumptive evidence now exists for cadmium having either mutagenic or carcinogenic effects; and it should be emphasized that such evidence is mainly based on observations obtained with very high exposure levels.

4.4 DOSE-EFFECT AND DOSE-RESPONSE RELATIONSHIPS OF CADMIUM IN HUMANS

Attempts to quantify the health impact of cadmium on man with regard to its potential effect on the United States population as a whole are discussed in this portion of the report. The discussion leans heavily on empirical data and theoretical approaches. The main concern will be with chronic exposure situations.

4.4.1 Dose Aspects

Dose, as defined on page 4-3, is taken to mean that amount of cadmium derived from either external or internal exposure.

The general population of the United States, as elsewhere, receives its major external exposure to cadmium via inhalation and ingestion. While estimates of the dietary intake of cadmium in various countries cover a wide range of values, current estimates of cadmium intake by ingestion in the United States range from 10 to 50 μg per day per person. Exposure via ambient air appears to be relatively negligible for the general population, but since cigarettes contain notable amounts of cadmium, large segments of the general population are exposed to additional burdens of cadmium via inhalation due to smoking (see 4.2, Exposure Aspects).

The relative values of various biological materials as internal indices of cadmium exposure have been reviewed (Friberg et al., 1974; Nordberg, 1976). As noted in the metabolism section, blood levels of cadmium after

administration to animals show a kinetic profile that includes rather rapid clearance followed by a slow rise, mirroring hepatic uptake and incorporation into metallothionein followed by release into the blood stream. Blood-cadmium values are therefore of little utility in reflecting critical-organ exposure under chronic conditions.

Urinary cadmium levels are probably more relevant in assessing internal chronic exposure. The animal studies of Nordberg (1972a, 1972b) and the human-subject data of Tsuchiya (1972a, 1972b), Johnson et al. (1977), and Elinder et al. (1978) indicate that in the absence of impaired renal-tubular function there is a correlation between urinary cadmium levels and the main storage organs for the element.

Hair-cadmium levels have not been shown to reflect well body burdens of cadmium and, as such, do not presently appear to be a useful exposure indicator.

4.4.2 Dose-Effect/Dose-Response Aspects

Various adverse health effects that have been associated with cadmium exposure were described extensively in Chapter 2 and summarized in Section 4.3 of the present chapter. In those previous discussions, the central focus was on qualitative characterization of pertinent health effects rather than a thorough quantitative assessment of relationships between cadmium exposure levels and associated pathophysiological outcomes. The present section will deal with quantitative aspects of cadmium exposure and its effects on health. In that regard, two main types of relationships must be considered: dose-effect and dose-response relationships.

Pfitzer (1976) drew the distinction between effect and response in the following terms: "Effect" is taken to indicate the variable change due to

a dose in a specific subject, and "response" is the number of individuals showing that effect, i.e., the number of "reactors" and "non-reactors" to the defined dose and specific effect in a group.

The kidney (kidney cortex) is generally accepted as being the critical organ for the chronic-exposure effect of cadmium; it is therefore appropriate to discuss data that define relationships between cadmium exposure and the effects of cadmium on renal function. In particular, proteinuria is typically taken as the main biochemical index of renal dysfunction induced by cadmium.

As for indices of cadmium exposure, blood cadmium levels cannot be used to assess the status of the critical organ in terms of that organ's direct exposure to the insulting agent. Urinary cadmium is a better index of overall cadmium exposure, but it is not a sufficiently good indicator of the extent of functional damage to the kidney to allow it to be a useful long-term diagnostic indicator of health impairment. Rather, the accumulation of cadmium in the kidney itself is presently generally accepted to be the best index of long-term cadmium exposure visa vis the definition of critical dose level(s) for induction of renal damage. Substantial attempts have, therefore, been made to define an approximate critical concentration of cadmium in the human kidney (kidney cortex) above which renal dysfunction can be expected to occur.

In regard to the definition of a critical concentration of cadmium in the kidney necessary for the induction of renal dysfunction, a range of estimates has been reported by different investigators. For example, as discussed in Chapter 2 of the present document, studies on the rat by Kawai and coworkers (Kawai and Fakuda, 1974; Kawai et al., 1974) found renal tubular atrophy and other morphological signs of kidney damage to be associated

with a kidney cadmium concentration of 150 μg/g wet weight. In addition, Nomiyama (1975) reported increased protein excretion in rabbits as occurring starting at an average kidney cadmium concentration of 200 μg/g wet weight, Suzuki (1974) observed proteinuria and increased urinary cadmium excretion at an average kidney cadmium cortex concentration of 225 μg/g wet weight.

Based on animal data of the above type and certain human autopsy data, Friberg et al. (1974) have proposed that 200 g/g wet weight of kidney cortex be considered as the critical concentration for cadmium-induced renal dysfunction, as indexed by proteinuria; and WHO (1977) and the Subcommittee on the Toxicology of Metals under the Permanent Commission and International Association of Occupational Health have tentatively endorsed this proposal (CEC, 1978). The selection of human autopsy data used to propose this level, however, has been criticized (Nomiyama, 1977).

More specifically, Nomiyama (1977) has noted that estimates of the critical concentrations might be more appropriately derived from cases where proteinuria was the only pathological finding, so that renal cadmium concentration measurements were less likely to have been affected by possible reductions in renal cadmium levels from those present at the onset of renal dysfunction. Such reductions in renal concentrations are known to occur due to increased outflow of kidney cadmium that commences sometime after the onset of renal tubular damage. Nomiyama (1977) noted that, from among the eight (Friberg, 1974) human cases reported with proteinuria only, renal cortex cadmium concentrations ranged from 21 to 395 μg/g wet weight, with all but one being at least 150 μg/g and four exceeding 300 μg/g. On this basis and other supporting data derived from studies on monkeys (Nomiyama, 1977), Nomiyama suggested that 300 μg/g may be a more accurate estimate than 200 μg/g for the critical concentration of

cadmium in renal cortex necessary for the induction of renal dysfunction as indexed by proteinuria.

Regardless of whether 200 or 300 μg/g is taken as being the better estimate of a theoretical critical concentration, it should be remembered that, in either case, a "typical" threshold cadmium concentration necessary to induce renal dysfunction is implied; but this may not fully reflect the wide individual variation in susceptibility for this damage consistently demonstrated to exist both in human and animal studies.

Given a specific value designated as an estimated critical concentration, it is possible, through the use of a metabolic model, to estimate the probable level of total cadmium exposure sufficient to produce the critical concentration in the renal cortex. In that regard, several such metabolic models have been developed using 200 μg/g (wet weight) in kidney cortex as the critical concentration.

Table 4-12 tabulates such values as obtained from Friberg et al. (1974), Nordberg (1974), and Kjellström (1976). Note that these values are based on two estimates of biological half-time of cadmium in kidney cortex: 18 and 38 years. Furthermore, the daily retention values (in μg) or daily maximum internal doses which are estimated to result in cadmium levels approaching the critical concentration in kidney cortex are presented as a function of exposure time. Given the relative amounts of absorption of cadmium via the respiratory (25 percent) and gastrointestinal tract (5 percent), levels of exposure via either inhalation or ingestion necessary to reach the critical concentration of 200 μg/g can be calculated. The inhalation values, are most pertinent for consideration of occupational exposure situations; they are also of utility in assessing the overall

Table 4-12. CADMIUM EXPOSURE REQUIRED FOR REACHING A KIDNEY CORTEX CONCENTRATION OF 200 μg Cd/g USING DIFFERENT ALTERNATIVES FOR BIOLOGICAL HALF-TIME IN KIDNEY CORTEX AND EXPOSURE TIME[a]

Basis of calculation[b]	Exposure time (yr)	Levels of cadmium uptake or retention yielding renal dysfunction, assuming cadmium half-time of: 38 yr	18 yr
		Daily retention (μg)	
Constant daily retention during whole exposure time	10	36	39
	25	16	20
	50	10	13
		Industrial air concentration ($\mu g/m^3$)	
25% pulmonary absorption, 10 m^3 inhaled per work day, 225 work days/year	10	23	25
	25	11	13
		Daily cadmium intake (μg)	
Food exposure for 50-year-old person (2500 ca/day) 4.5% retention) (changing caloric intake by age accounted for)	50	250	360
		Corresponding average concentration in foodstuffs (μg/g)	
Total amount (net weight) of food/day 300 g	50	0.8	1.2
600 g		0.4	0.6
1000 g		0.25	0.35

[a]Modified from Friberg et al., 1974.

[b]Assumptions: one-third of whole body retention reached kidney and kidney cortex concentration 50% higher than average kidney concentration. From Nordberg (1976).

validity of the model by comparing predicted with actual occupational-assessment results. For populations at large, the data for total dietary intake limits are more important. The values given in the table are 250 and 360 μg for both estimated half-times of cadmium for individuals 50 years of age.

This simple model approach, however, has limitations as pointed out by Nordberg (1976) and in order to assess its validity, it is obviously necessary to evaluate the correspondence of results predicted by the model to actual observed data. That is, it would be useful to compare predicted and actual exposure values for inhalation of amounts of cadmium resulting in increased incidence of proteinuria in workers or for ingestion of foodstuffs of known cadmium content in population groups showing evidence (proteinuria) of renal dysfunction.

Friberg et al. (1974) concluded that in man lethal, acute exposure to a cadmium level in air is somewhat less than 5 mg/m^3 for an 8-hr period, whereas emphysema, a chronic respiratory effect, appears to occur when the air level value is about 0.1 mg/m^3 and probably lower (66 $\mu g/m^3$) in the case of workers who smoke (Lauwerys et al., 1974). In contrast, Kjellström (1976) has complied data relating estimated air exposure of workmen to cadmium and the incidence of proteinuria, and it appears that the incidence of proteinuria is significantly elevated after 10 to 20 years at an occupational air exposure level as low as 50 $\mu g/m^3$.

Kjellström (1976) also evaluated epidemiological data for the occurrence of proteinuria in Japanese populations residing in identified, high-cadmium-exposure areas. The data in this case are valuable in that, in most cases the exposure was dietary, and a number of the studies surveyed had measured

the cadmium level of the chief dietary component. The results obtained corresponded well with estimates of 250 to 360 μg/day based on the above metabolic model. Consistent with Kjellström's (1976) findings, a WHO working group (WHO, 1977) analyzed epidemiological data from Japan and concluded that an average daily dietary intake of 300-480 μg would cause the critical level for renal damage to be reached. Lower estimates of daily dietary intake levels necessary for the critical renal cortex concentration to be reached, however, have been proposed by others. For example, the Working Group of Experts for the Commission of European Communities (CEC, 1978), using two different approaches, arrived at estimates of 200 and 248 μg/day for nonsmokers. The effect of smoking can be seen in that the estimate derived for smokers using the first approach, 169 μg/day, was distinctly lower than the 200 μg/day for non-smokers.

Thus far, in the present discussion of dose-effect and dose-response relationships, we have focused on various modeling approaches used to define dose-effect relationships. Such approaches, as seen above, both seek to define a critical concentration of cadmium in the kidney for the induction of renal dysfunction and, also, "threshold" external exposure values for either inhalation or ingestion of cadmium that will result, over long periods of time (10, 25, 50 years), in the critical concentration for renal dysfunction being reached. They are useful in helping to conceptualize dose-effect relationships for cadmium-induced renal damage in that: (1) they provide a theoretical framework within which complex interrelationships between external exposure doses (via inhalation or ingestion), internal exposure levels (as indexed by renal cadmium levels), and consequent renal

dysfunction (indexed by proteinuria) can be stated in a simplified manner; (2) also, as such, they provide one means for trying to predict critical levels of external exposures that would result in the induction of renal damage in humans; and (3) they allow for empirical verification of their accuracy in terms of comparison of predicted versus observed values for pertinent parameters.

The above types of modeling approaches, however, have their limitations, as noted earlier, and should be viewed visa vis their utility within the context of what their limitations allow. Among the more crucial points to be remembered is that such models do not allow for one to adequately take into account individual biological variation in regard to the relationships characterized by the models. For example, in calculating external exposure levels necessary for reaching a certain renal cadmium concentration, average absorption or retention rates for cadmium intake via inhalation or ingestion are used. Specific individuals, however, it should be emphasized, have absorption or retention rates that vary from the average, some being much lower and others much higher. Thus, a given external exposure level may produce a relatively low renal cadmium accumulation in one person while the same exposure level can result in a much higher renal accumulation in another individual. Similarly, certain renal accumulations could be associated with renal damage for the most susceptable members of a human population at levels distinctly lower than those producing such damage "on the average."

Based on the above considerations, it is, therefore, conceivable that a relatively low external exposure level could result in a renal cadmium accumulation for one individual distinctly above the average for a group;

and, also, that renal accumulation, while low in comparison to the average level necessary to induce renal dysfunction, could nevertheless result in significant renal damage for the given individual. Conversely, some individuals, the least susceptable ones in a population, may not experience renal damage even at exposure levels much higher than the average level yielding such damage for most members of the population. The existence of wide variability in individual dose-effect relationships for cadmium-induced renal damage is hinted at, for example, by the range of renal cortex cadmium concentrations (21 to 395 μg/g wet weight) reported by Nomiyama (1977) to be associated with proteinuria, as discussed earlier. It is, therefore, important in any risk assessment for cadmium-induced renal damage to take into account such individual variability and to consider what proportion of a target population will show signs of renal dysfunction at various cadmium exposure levels. Progress in defining such dose-response relationships has been accomplished recently, as reported by Kjellström (1977).

Kjellström (1977) reported a detailed assessment of dose-response in man involving both calculated and epidemiological data and using renal tubular dysfunction indexed by β_2-microglobulin excretion as the adverse health effect. In Figure 4-5 are depicted calculated (lines) and observed (symbols) dose-response relationships for cadmium-induced increase of urinary β_2-microglobulin excretion. It should be noted that the actual response rates fit rather well with the modeling results, the actual rates being obtained from three separate study groups. The abscissa expresses exposure as daily intake of cadmium multiplied by an assumed 50-year period of exposure, while the ordinate shows both percent population affected and the corresponding probits. The numerical values besides the lines are for

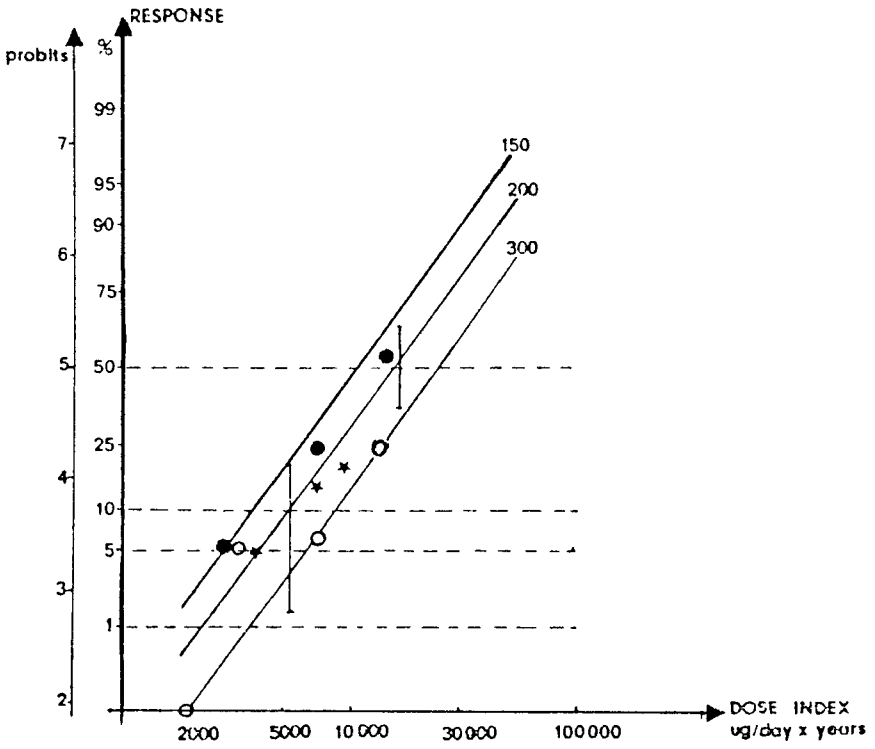


Figure 4-5. Calculated (lines) and observed (symbols) dose-response relationships for cadmium-induced increase (>97.5 percentile of reference group) of urinary β_2-microglobulin excretion. (From Kjellström, 1977)

three renal cortex "critical concentration" cadmium values: 150, 200, and 300 μg/g net weight. If one selects as a critical concentration a renal cortex value of 200 μg cadmium/g wet weight kidney cortex, the affected proportions of a population group as a function of daily dietary intake of cadmium can be predicted as shown in Table 4-13.

The Kjellström table (4-13) takes into account the varying kidney and body sizes of Europeans and Japanese and presents the values for a response rate at age 50. Note that at a dietary intake level as low as 60 μg/day, average-sized adult Americans would be predicted to show a 1.0 percent response rate and, by 100 μg/day, approximately 5 percent would be predicted to exhibit renal proteinuria as indexed by increased β_2-microglobulin excretion. As Kjellström has noted (Kjellström, 1977), these predicted dose-response values are based on a number of assumptions which must be viewed with caution. Given the good agreement seen in Figure 4-5 between predicted and observed values, however, they may be reasonable estimates of response rates likely to be observed at various average levels of daily dietary cadmium intake at least at levels above 80 to 100 μg/day where the largest numbers of observed data points pertain.

Nogawa et al. (1978) also present data on cadmium induced renal dysfunction which may be used to define dose-response relationships; in this case excretion of retinol binding protein (RBP > 4 mg/l) was used to define renal tubular proteinuria. Data on cadmium in rice and RBP in urine (Table 4-14) showed a consistent increase in renal tubular proteinuria for every rice cadmium concentration category greater than the controls. Examining the data on an age basis (50-59, 60-69, and 70+ years), one can see the effects of cadmium accumulation on the prevalence of renal tubular

TABLE 4-13. Food exposure; calculated intakes (μ/day) that may give a certain response rate at age 50.[a]

	Response rate (proportion) with renal tubular damage)					
	0.1%	1%	2.5%	5%	10%	50%
Europeans, body weight 70 kg.	32	60	80	100	148	440
Japanese, body weight 53 kg.	24	44	60	76	100	325

[a]Gastrointestinal absorption rate 4.8%, Non-smokers (From Kjellström (1977)).

Table 4-14. PREVALENCE OF TUBULAR PROTEINURIA AND SUSPECTED PATIENTS AMONG ADULTS MORE THAN 50 YEARS OF AGE IN RELATION TO VILLAGE AVERAGE RICE CADMIUM CONCENTRATIONS

Village average rice cadmium concentration (μg/g)			Urinary excretion of retinol binding protein			Suspected patient (percent)	Tubular proteinuria, amino aciduria[e] and decreased TRP%[f] (percent)
			Greater than (±)[b] (percent)	Greater than ±[c] (percent)	Greater than +[d] (percent)		
Polluted village	Mean	N[a]					
0.19 - 0.29	(0.24)	1122	4.55*	3.39*	1.52	1.25	0.27
0.30 - 0.39	(0.38)	413	7.02**	4.84**	2.66*	2.66**	0.24
0.40 - 0.49	(0.45)	616	5.84**	4.22**	2.76**	3.25**	0.97
0.50 - 0.59	(0.56)	353	13.03**	11.61**	8.50**	6.80**	1.98*
0.60 0.69	(0.65)	140	30.00**	24.29**	14.29**	12.1**	5.71**
Control		248	1.21	0.81	0.40	0	0

[a] Number of persons examined.
[b] Around 4 mg/liter.
[c] Around 8 mg/liter.
[d] Around 16 mg/liter.
[e] Proline; more than 10 mg/liter. Amino N; more than 300 mg/g creatinine.
[f] Less than 80 TRP%.
* Significant difference (P<0.05) compared with control.
** Significant difference (P<0.01) compared with control.

Source: Nogawa et al. (1978)

proteinuria at every exposure dose level studied (Table 4-15). Thus, at cadmium levels as low as 0.19 to 0.29 μg/g of rice, statistically significant increases in prevalence of tubular proteinuria over that seen with control levels of cadmium in rice were reported in the oldest age group studied (i.e., the 70+ group). Dietary rice levels of 0.19 to 0.29 μg/g can be estimated to result in an equivalent total dietary cadmium intake of 96 to 147 μg/day, based on assumptions and calculations reported by Ryan (1978).

4.5 POPULATIONS AT RISK TO EFFECTS OF CADMIUM

Population at risk is that segment of a defined population exhibiting characteristics associated with a significantly higher probability of developing a condition, illness, or other abnormal status. This higher risk may result from either greater inherent susceptibility or from exposure situations peculiar to that group. Inherent susceptibility refers to some host characteristic or status which predisposes that host to a heightened response to an external stimulus or agent.

The collective Japanese experience with water- and airborne cadmium pollution can be cited as one example where many factors placing particular groups at risk for cadmium-induced renal damage have been identified. Working back from demonstrated heightened vulnerability in Japanese subgroups of populations may therefore allow American populations at risk to be identified as well.

Japan is, to date, the only known location where cadmium exposure was/is high enough to affect significant groups of the regional population in those areas of cadmium pollution via water and/or air. In the Japanese experience with cadmium, the clinical extreme of which is Itai-Itai

Table 4-15. PREVALENCE OF TUBULAR PROTEINURIA IN RELATION TO AGE AND VILLAGE AVERAGE RICE CADMIUM CONCENTRATION

Age	Greater than RBP (±)						Greater than RBP (±)					
Cd in rice	50 - 59		60 - 69		≥70		50 - 59		60 -69		≥70	
(microgram per gram)	N[a]	Percent	N[a]	Percent	N[a]	Percent	N[a]	Percent	N[a]	Percent	N[a]	Percent
Control	104	0.96	80	2.50	64	0.00	104	0.00	80	1.25	64	0.00
0.19 - 0.29	477	0.84	377	2.65	268	13.81**	477	0.42	377	0.80	268	4.48
0.30 - 0.39	184	3.26	138	5.07	91	17.58**	184	2.72	138	0.72	91	7.69*
0.40 - 0.49	295	1.69	204	6.86	117	14.53**	295	0.34	204	2.94	117	8.55**
0.50 - 0.59	140	0.71	120	10.83*	93	34.41**	140	0.00	120	5.00	93	25.81**
0.60 - 0.69	60	18.33**	57	24.56**	23	73.91**	60	5.00*	57	12.28**	23	43.48**

[a] Number of persons examined.
* Significant difference (P<0.05) compared with control.
** Significant difference (P<0.01) compared with control.

Source: Nogawa et al. (1978)

disease, the individuals found to be most vulnerable to the effects of cadmium were post-menopausal women with a history of multiple childbirths as well as calcium and Vitamin-D deficiency. This hints, in part, at women in general possibly being at special risk. However, Itai-Itai disease, per se, has not been observed conclusively in all of the exposure areas in Japan revealed so far. This finding would also seem to point to nutritional status as being an important determinant in placing certain groups at special risk for the adverse health effects of cadmium.

In addition to the above, a consistent finding in most of the cadmium-polluted areas of Japan has been the factor of age as a determinant in the prevalence of proteinuria, a measure of renal dysfunction, with proteinuria being observed most often in groups above 40 years of age. Thus, older members of any population appear to be more at risk in any demonstrated or potential cadmium-exposure setting, with those having nutritional deficits exhibiting the highest risk.

Perhaps even more importantly for present purposes, however, given that the gradual accumulation of cadmium in the renal cortex over a long period of time (e.g., 20 to 50 years) is a key factor in inducing renal dysfunction in humans, then the entire population must be considered as being at potential risk for such effects over their lifetimes. Thus, as a starting point, current dose-response relationships for the United States population in general must be defined. Then, particular groups at special risk beyond that existing for the general population need to be delineated.

In order to assess the potential impact of various cadmium exposure situations on the health of the United States population, a dose-response model must be derived which relates existing American cadmium exposure

levels to predicted response rates for renal dysfunction. Of greatest importance here are considerations of dietary cadmium intake as the single most important source of cadmium exposure for the general United States population. In regard to estimates of current daily dietary cadmium intake for Americans, it was earlier (Section 4.2.4) noted that different estimation approaches indicate that the average daily dietary intake for Americans presently falls within the range of 10 to 50 μg/day.

It was also noted earlier (Section 4.4.2) that several different approaches have been used for estimating dietary intake levels expected to result in a critical renal cortex cadmium concentration associated with renal dysfunction being reached over a 50-year exposure period. Using certain metabolic model approaches, estimates ranging from 200 to 480 μg/day have been generated from nonsmokers; however, values at the lower end of that range, i.e., 200 to 248 μg/day, have been accepted as the best estimates by a Working Group of Experts for the Committee of European Communities (CEC, 1978). If the latter estimates are accurate, then current average American dietary intake levels of 10 to 50 μg/day would be anywhere from four to twenty times lower than levels yielding a critical renal cortex cadmium concentration associated with renal dysfunction. On the other hand, certain presently available information strongly suggests that such a large margin of safety does not exist for the most susceptible members of the general United States population.

More specifically, as discussed earlier under Section 4.4.2, Kjellström's (1977) modeling of predicted dose-response relationships and actual observed data confirming the accuracy of the model suggest that as much as 1 percent of the general United States population may exhibit signs (proteinuria) of

renal tubular damage at a daily dietary cadmium intake level of 60 μg/day. The same model predicts expected response rates of 2.5 percent and 5 percent at dietary intake levels of 80 and 100 μg/day, respectively. Viewed from this latter perspective, then, current estimated United States dietary intake levels of 10 to 50 μg/day would range from being less than two to about eight times less than intake levels yielding renal dysfunction for significant portions of the general population as a consequence of 50 years of dietary cadmium exposure.

The above information suggests that some members of the general population may already have daily dietary cadmium ingestion levels that approach those likely to yield renal tubular dysfunction in old age (i.e., after a 50-year exposure period). In addition to this element of risk potentially present for the general United States population, a distinctly higher level of risk for cadmium-induced renal dysfunction has been rather conclusively shown to exist for individuals that smoke cigarettes.

In an earlier portion of this Risk Assessment section (Exposure Aspects, 4.2) the relative contribution of smoking to daily cadmium retention as a function of increasing cigarette use was tabulated. In Table 4-16, significant increments in daily retained amounts (daily increase in burden) of cadmium can be seen to arise from cigarette smoking, the relative values being particularly striking if one takes 25 μg/day as the average intake arising from food. Assuming a daily intake of 25 μg, smoking one, two, or three packs of cigarettes a day furnishes percentages of 40, 62, and 71 percent, respectively, of daily cadmium retention for smokers. Even in the case where 50 μg/day is the dietary intake of cadmium, the smoking of two packs of cigarettes daily roughly doubles the daily total retention. In Table

Table 4-16. RELATIVE CONTRIBUTION OF CIGARETTE SMOKING TO TOTAL DAILY CADMIUM RETENTION[a]

Cigarette packs/day	Daily food intake of 50 μg	Daily food intake of 25 μg
0	0	0
1/2	18	29
1	30	40
2	47	62
3	57	71

[a]Daily cadmium retention for water and air, 0.24 μg total. (See Table 4-11.)

4-17 are given the relative contributions of smoking to total daily cadmium intake as a function of different ambient air levels and varying dietary intake levels (25, 50 and 75 μg/day) reflecting current and expected future intake levels in the United States.

If one now relates these values to the table (Table 4-12) containing figures for the estimated level of daily retention of cadmium as a function of exposure time (first part of Table 4-12), above which the critical concentration for renal dysfunction is reached at the end of the exposure period, a significant risk among smokers in approaching these retention limits (10 μg/day) becomes apparent, even assuming only the two lowest dietary intake levels.

In Table 4-18 are given the relative amounts of the critical daily cadmium retention values achieved with smoking at two exposure times (Table 4-12) and employing the half-time (38 years) giving the lower critical retention figure.

In the case of a daily intake of 50 μg cadmium in food (3.0 μg net retention), an individual smoking two packs per day throughout his adult lifetime approaches two-thirds of the critical retention level (10 μg) at age 70, assuming smoking started at age 20.

In Table 4-18, an ambient air cadmium level of 30 ng/m^3 was chosen, using the example in Table 4-11. If one also tabulates the relative contributions of ambient air cadmium over the range 1 to 1,000 ng/m^3 taking into account retention from cigarette consumption, one arrives at the figures in Table 4-19. At ambient air levels of 1 and 10 ng/m^3, no air contribution is made that significantly enhances the risk of smokers over that arising from diet and cigarettes. At levels of 100 ng/m^3, however, a

Table 4-17 ESTIMATED RELATIVE CONTRIBUTION OF DIETARY INTAKE, CIGARETTE SMOKING AND AMBENT AIR CADMIUM LEVELS TO TOTAL DAILY CADMIUM RETENTION FROM ALL SOURCES[a]

Dietary Intake (Net Retention)	Smoking Status (Net Retention)	Air Cadmium Levels (Net Retention) 0.0 ng/m^3 (0.0 μg/day)	1.0 ng/m^3 (.0005 μg/day)	10 ng/m^3 (.005 μg/day)	100 ng/m^3 (.05 μg/day)	1000 ng/m^3 (0.5 μg/day)
Food Level A = 25 μg/day (1.50 μg/day)	Non-smoker (0.00 μg/day)	1.590 (0;0%)*	1.591 (0;0%)	1.595 (0;0%)	1.630 (0;3%)	2.090 (0;24%)
	½ pack/day (0.70 μg/day)	2.290 (31;0%)	2.291 (31;0%)	2.295 (31;0%)	2.330 (30;2%)	2.790 (25;18%)
	1 pack/day (1.41 μg/day)	3.000 (47;0%)	3.001 (47;0%)	3.005 (47;0%)	3.050 (46;1%)	3.500 (40;14%)
	2 pack/day (2.82 μg/day)	4.410 (64;0%)	4.411 (64;0%)	4.415 (64;0%)	4.460 (63;1%)	4.910 (57;10%)
	3 pack/day (4.22 μg/day)	5.810 (73,0%)	5.811 (73;0%)	5.815 (73;0%)	5.860 (72;1%)	6.310 (67;8%)
Food Level B = 50 μg/day (3.00 μg/day)	Non-smoker (0.00 μg/day)	3.090 (0;0%)	3.091 (0;0%)	3.095 (0;0%)	3.140 (0;2%)	3.590 (0;14%)
	½ pack/day (0.70 μg/day)	3.790 (18;0%)	3.791 (18;0%)	3.795 (18;0%)	3.840 (18;1%)	4.290 (16;12%)
	1 pack/day (1.41 μg/day)	4.500 (31;0%)	4.501 (31;0%)	4.505 (31;0%)	4.550 (31;1%)	5.000 (28;10%)
	2 pack/day (2.82 μg/day)	5.910 (48;0%)	5.911 (48;0%)	5.915 (48;0%)	5.960 (47;1%)	6.410 (44;8%)
	3 pack/day (4.22 μg/day)	7.310 (58;0%)	7.311 (58;0%)	7.315 (58;0%)	6.360 (57;1%)	7.810 (54;6%)
Food Level C = 75 μg/day (4 50 μg/day)	Non-smoker (0.00 μg/day)	4.590 (0;0%)	4.591 (0.0%)	4.575 (0;0%)	4.640 (0,1%)	5.090 (0;10%)
	½ pack/day (0.70 μg/day)	5.290 (13;0%)	5.291 (13;0%)	5.295 (13;0%)	5.340 (12;1%)	5.790 (12;9%)
	1 pack/day (1.41 μg/day)	6.000 (24;0%)	6.001 (24;0%)	6.005 (24;0%)	6.050 (23;1%)	6.500 (22;8%)
	2 pack/day (2.82 μg/day)	7.410 (38;0%)	7.411 (38;0%)	7.415 (38;0%)	6.460 (38;1%)	7.910 (36,6%)
	3 pack/day (4.22 μg/day)	8.810 (48;0%)	8.811 (48;0%)	8.815 (48;0%)	8.860 (48;1%)	9.310 (45,5%)

[a]Note that a total daily retention level of 10 μg/day would be expected to yield renal dysfunction over a 50-year exposure period.

*Each first value equals total daily cadmium retention levels (in μg/day) from all sources, assuming constant daily retention from water of 0.09 μg/day derived from consumption of water with cadmium concentration of 1 ppb. The two values in parentheses ( ) indicate percentage of total daily cadmium retention attributed to cigarette smoking and ambient air cadmium exposure, respectively, at a given ambient air cadmium level.

Table 4-18. PERCENTAGE OF CRITICAL DAILY CADMIUM RETENTION LEVEL YIELDING RENAL DYSFUNCTION ACHIEVED BY SMOKERS AT TWO EXPOSURE TIMES AND TWO DIETARY LEVELS[a,b,c]

Cigarette consumption (packs/day)	Exposure period and diet intake			
	25 Years		50 Years	
	Food Level A (25 μg/day)	Food Level B (50 μg/day)	Food Level A (25 μg/day)	Food Level B (50 μg/day)
0	20	32	11	17
1/2	25	39	15	24
1	29	47	20	32
2	38	61	28	46
3	47	75	38	60

[a]Food A, 50 μg cd/day intake, 3.0 μg cd retained.
Food B, 25 μg cd/day intake, 1.5 μg cd retained.

[b]Combined air and water retained cadmium value = 0.24; Table 4-11.

[c]Critical daily cadmium retention level for induction of renal dysfunction = 10 μg/day for 25-year exposure period.

Table 4-19. PERCENTAGE OF CRITICAL DAILY CADMIUM RETENTION LEVEL YIELDING RENAL DYSFUNCTION ACHIEVED BY SMOKERS AS A FUNCTION OF AMBIENT AIR CADMIUM LEVELS[a,b]

Cigarette packs/day	Daily food intake of:	Ambient air (ng/m^3) 0		1.0		10.0		100.0		1,000.0	
		25 μg	50 μg	25 μg	50 μg	25 μg	50 μg	25 μg	50 μg	25 μg	50 μg
0		16	31	16	31	16	31	21	36	66	80
1/2		23	38	23	38	23	38	28	43	73	87
1		30	45	30	45	30	45	35	50	80	94
2		44	59	44	59	44	59	49	64	87	101
3		58	73	58	73	58	73	63	78	94	108

[a]Assuming daily cadmium retention from water of .09 μg/day.
[b]Exposure period of 50 years.

uniform increase of 5 percent is seen, with the increase in percentage at 1,000 ng/m^3 then going to 50 percent over that of no ambient air levels of cadmium.

Experimental data in support of considering smokers as being at increased risk for the renal effects of cadmium are available from human autopsy studies of organ cadmium levels, particularly kidney cadmium levels. These studies are described in the Human Epidemiology section and show that smokers have kidney levels of cadmium considerably above those for non-smokers, up to twice the relative amount.

In the Exposure Aspects portion of this chapter, mention is made of the growing use of sludge material dispersed on agricultural lands. Furthermore it was pointed out that this material is often enriched in cadmium relative to soils in general and, therefore, its use may result in significantly increased cadmium levels in soil, food crops grown on the sewage-treated soil, and consumer-distributed food products derived from such crops. If this be the case, then one must consider as a potential population at risk in the United States, those who may be so placed at risk by virtue of dietary habits, in particular those for whom grains and leafy vegetables comprise the sole or major portion of their diet. These foodstuffs are particularly adept at taking up cadmium from soils.

Lucas et al. (1978) have suggested that sludges with less than 60 ppm cadmium can be applied at maximum rates to meet crop nitrogen requirements and still produce acceptable levels of cadmium in vegetables, assuming 110 μg/day of cadmium ingestion via food to be safe. Factors which complicate any quantitative assessment of the risk impact of cadmium-containing sludge are population mobility and a centralized food marketing and distribution

system that would have some diluting effect on high cadmium vegetables and grains. Still, increased dietary cadmium levels of any amount must be considered as further increasing the risk of population groups already at special risk, such as old people, vegetarians or smokers (as is illustrated for the latter in the bottom half of Table 4-17).

Scrutiny of the literature with reference to those individuals on the other end of the age scale, young children, furnishes very limited hard evidence of a clinical epidemiological nature that children may presently be considered a group at special risk for the health effects of cadmium. As implied in EPA's Air Quality Criteria for Lead (1977), however, children, by virtue of their relationship to their exposure setting and to their differences in metabolic functions, may be at invariably greater risk for any toxic metal that parallels lead's distribution in the environment, particularly in dustfall. The "mouthing" activity of young children, a normal behavioral trait, would expose this group to non-foodstuffs such as cadmium-containing dust and dirt. Furthermore, there is the question of enhanced absorption and, more important, possible enhanced retention.

Bogden et al. (1974) studied the extent of exposure of a group of urban children to cadmium. These workers found a significant positive correlation between cadmium and lead ($p<0.006$) and between cadmium and zinc ($p<0.001$). These correlations suggest that, since increased lead concentrations in blood occur because of environmental contamination, then cadmium is being co-absorbed with the lead. While paint could be a source of both cadmium and lead, the zinc/cadmium correlation is more vexing as to source. As part of their study, they correlated the mean atmospheric concentrations of each element for a specific year and found strong positive correlations between the three pairs ($p<0.01$): cadmium/lead, zinc/lead

and zinc/cadmium, indicating to these investigators that inhalation may be a factor in the blood values. Delves et al. (1973) in their study, however, could find a correlation of only 0.05 for lead and cadmium or between zinc and cadmium.

The hazard posed to children in this type of exposure setting may be heightened for several reasons:

(1) Many children in urban areas, particularly those of lower socio-economic status, have a greater incidence of calcium, iron, and zinc deficiency, which are states that could enhance the effects of cadmium (see 2.16, Interactions section).

(2) Co-exposure of children to lead and cadmium may heighten the health effect of either or both through synergism.

(3) We know that industrial use of cadmium in urban areas adds to the dust and soil burden via fallout (see 4.2, Exposure Aspects) and to the exposure of children in these areas via "mouthing" activity, etc.

Another group within the general population of the United States who may be at increased risk are those whose water supplies are soft or acid. Soft water has been associated with heightened occurrence of cardiovascular disease (see 2.6 of the Health Effects section). While hypertension induced experimentally by cadmium has been established, at present the parallel data for humans do not conclusively show an etiological role for cadmium in human hypertension. This is an important issue and, like the case with children, requires more research.

The risk posed by cadmium to pregnant women, more specifically the fetus, is another area of concern. It has been shown, as described in the health effects section on reproduction and development, that although

cadmium passes the placental barrier in only small amounts, it nevertheless can affect the birth weights and morphological development of offspring exposed _in utero_ through dosing of the mother. Such prenatal effects on fetal development also appear to persist into postnatal development and seem to occur secondarily to cadmium effects on the mother, e.g., in causing decreased levels of essential elements such as zinc, iron, and copper.

In light of the animal studies demonstrating such cadmium effects, the findings of Cvetkova (1970) on women in the U.S.S.R. occupationally exposed to cadmium oxide are quite interesting. Those women had normal courses of pregnancy and deliveries, but their children had lower birthweights when compared with those of control workers. Such results are consistent with those repeatedly found in animal studies where reduced birthweight is often observed. Thus there appears to be a reasonably well-established relationship between cadmium exposure during pregnancy and reduced birth weights. This adverse effect and a less well-demonstrated association with stillbirths argues for pregnant women being a special group at risk to cadmium by virtue of potential deleterious effects on the fetus.

Several studies provide further evidence for children continuing to be at risk well beyond the neonatal periods of their life. Higher than "normal" levels of cadmium have been demonstrated in children as a function of: (1) increasing age (Delves _et al._, 1973; Gross _et al._, 1976) and (2) suspected pica and geographic location of residence, with inner-city children having higher levels than others (Bogden _et al._, 1974). The health implications of such cadmium exposures in children remain to be better established, as discussed elsewhere in the section on human epidemiology; but one must suspect that the general consequence would be that of putting them at

higher risk for any of the many adverse health effects described earlier under the section on health effects. One interesting hint of possible adverse consequences of cadmium exposure in children comes from the study by Pihl et al. (1977) discussed earlier as showing an association between cadmium levels in the hair of children and incidence of mental retardation.

4.6 UNITED STATES POPULATION GROUPS IN RELATION TO PROBABLE CADMIUM EXPOSURES

This section is concerned with the numbers of individuals potentially at risk to cadmium exposures. It is not possible to delineate well all of the members of those segments of the United States population that would fit the potential risk categories described in the previous section on populations at risk.

Table 4-20 presents estimates from EPA's Cadmium Population Exposure Analysis (1978) of the numbers of individuals in the U.S. population exposed to airborne cadmium levels >0.1 ng/m^3 as a function of average cadmium exposure and type of cadmium source. In terms of numbers of individuals exposed, those in proximity to municipal incinerators constitute the largest group and are exposed to an average level of 7.2 ng/m^3. Comparatively smaller, though significant, populations are exposed to higher air levels (10 ng/m^3), however, by virtue of residence near other cadmium-emitting point sources. Iron and steel production result in the second largest group of individuals exposed, about 20 million. It should be noted that, although large numbers of individuals are exposed via inputs from such sources into the ambient air, the average exposure levels present, except perhaps for those very close to high emitting point sources, generally do not appear to be associated with increased risk for any particular health effect.

Table 4-20. AVERAGE EXPOSURE AND NUMBER OF PEOPLE EXPOSED TO ANNUAL CADMIUM LEVELS GREATER THAN 0.1 ng/M^3 BY SPECIFIED SOURCE TYPES[a]

Source type	Average exposure (ng/m^3)[b]	# of people exposed (10^3 people)
Secondary copper	2.3	6,484
Secondary zinc	0.4	9
Municipal incinerators	7.2	49,026
Primary zinc	10[c]	449
Primary lead	10[c]	46
Primary copper	10[c]	620
Primary cadmium	10[c]	245
Iron and steel	1.8	19,947
Total		76,826

[a]Adapted from Cadmium Population Exposure Analysis (EPA, 1978).

[b]0.1 ng is lower limit of detectability with current instrumentation.

[c]Preliminary estimate, not based on actual modelling results.

Table 4-21. COMPARISON OF CADMIUM EXPOSURES AMONG SOURCES (10^6 Nanograms-Person-Year)[1]

Source type	Total
Secondary copper	15.1
Secondary zinc	0
Municipal incinerators	350.8
Primary zinc	4.5
Primary lead	.5
Primary copper	6.2
Primary cadmium	2.5
Iron and steel	35.2
Total[2]	414.8

[1]Computed by multiplying the population exposed to each source by the concentrations resulting from that source. Adapted from Cadmium: Population Exposure Analysis (EPA, 1978).

[2]May not sum due to independent rounding.

Table 4-22 POPULATION EXPOSED TO CADMIUM CONCENTRATIONS (10^3 people)[a]

Source type	Annual concentration (ng/m^3)			
	>10	>5	>1	>0.1
Secondary copper				
Type 1[b]	189	517	3,580	6,484
Type 2[c]	189	517	3,580	6,484
Secondary zinc				
Type 1	0	0	0	9
Type 2	0	0	0	9
Municipal incinerators				
Type 1	1,665	26,576	99,123	174,871
Type 2	1,665	9,038	34,376	49,026
Primary zinc				
Type 1				449[d]
Type 2				449[d]
Primary lead				
Type 1				46[d]
Type 2				46[d]
Primary copper				
Type 1				620[d]
Type 2				620[d]
Primary cadmium				
Type 1				245[d]
Type 2				245[d]
Iron and steel				
Type 1	378	984	6,172	27,103
Type 2	372	910	5,601	19,947
Total				
Type 1	2,232	28,077	108,875	209,827
Type 2	2,226	10,465	43,827	76,817
Type 3[e]	2,226	10,465	38,530	65,021

Table 4-22 (cont.)

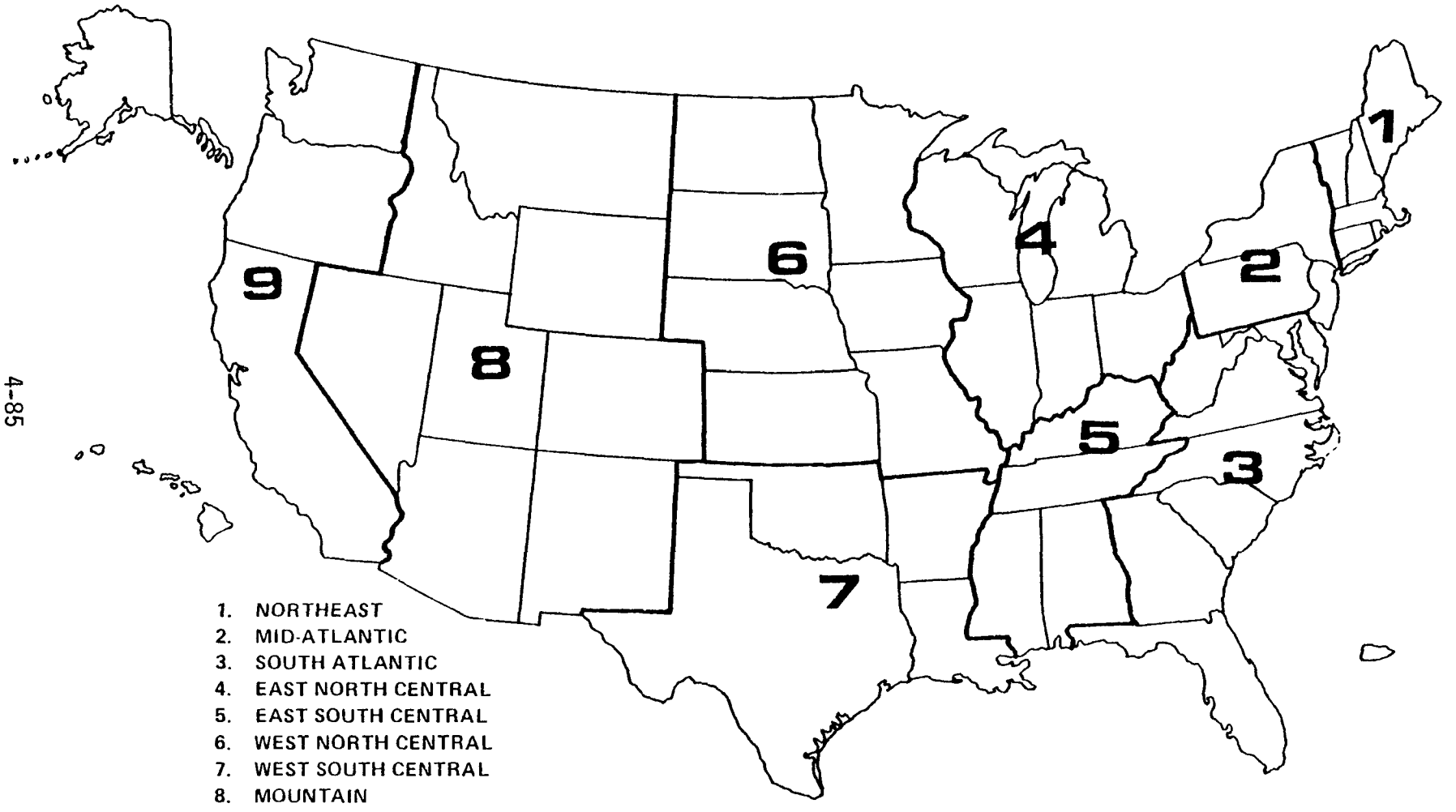
[a]Adapted from Cadmium: Population Exposure Analysis (EPA, 1978).

[b]Type 1 results are the sum of population exposed to higher than the specified concentration. Significant "double counting" may exist.

[c]Type 2 results represent the population exposed to greater than the specified concentration from at least one point source within each category. Double Counting within source categories eliminated.

[d]Actual concentrations not specified due to modelling problems. People represent population within 20 Km of a plant.

[e]Type 3 results represent the population exposed to greater than the specified concentration from at least one point source. All double counting eliminated.



1. NORTHEAST
2. MID-ATLANTIC
3. SOUTH ATLANTIC
4. EAST NORTH CENTRAL
5. EAST SOUTH CENTRAL
6. WEST NORTH CENTRAL
7. WEST SOUTH CENTRAL
8. MOUNTAIN
9. PACIFIC

[a]Coleman, 1977.

Figure 4-6. Regions Used in Cadmium Analysis.[a]

Table 4-23. REGIONAL BREAKDOWN ON POPULATION[1] EXPOSED TO CADMIUM CONCENTRATIONS GREATER THAN 0.1 NANOGRAMS PER CUBIC METER FROM SELECTED STATIONARY SOURCES (1,000 POPULATION)[2]

Source type	Region[3]									
	1	2	3	4	5	6	7	8	9	Total
Secondary copper	1,434	0	0	1,889	0	313	1,027	213	1,608	6,484
Secondary zinc	0	0	0	4	0	0	5	0	0	9
Municipal incerators	6,570	19,873	6,239	12,501	787	1,760	1,122	173	0	49,026
Primary zinc	0	359	0	0	0	0	73	17	0	449
Primary lead	0	0	0	0	0	0	0	46	0	46
Primary copper	0	0	19	3	0	0	0	137	461	620
Primary cadmium	0	100	0	87	0	0	41	17	0	245
Iron and steel mills[4]	93	4,743	2,410	8,710	649	108	1,626	0	1,607	19,947
Total	7,671	22,748	7,379	15,259	1,238	1,604	1,718	481	3,543	61,640

[1]Population figures rounded to nearest thousand.

[2]Adapted from Cadmium: Population Exposure Analysis (EPA, 1978).

[3]See Figure 1 for regional breakdowns.

[4]Includes all configurations of iron and steel mills.

[5]Double counting eliminated.

Table 4-24 NUMBER OF BIRTHS BY RACE AND SIZE OF POPULATION

Urban areas by population size	Births, 1970[a]			
	White	Black	Other	Total
≥1000,000	772,230	321,412	24,394	1,118,036
50-99,999	286,706	37,024	4,182	327,912
10-49,999	600,166	65,790	10,394	676,350
≥9,999	1,432,162	148,136	28,790	1,609,088
Total	3,091,264	572,362	67,760	3,731,386

Urban areas by population size	Births, 1975[b]			
	White	Black	Other	Total
≥100,000	571,478	276,387	26,332	874,197
50-99,999	222,735	37,885	5,921	266,541
10-49,999	478,382	64,481	13,039	555,902
≤9,999	1,279,401	132,828	35,329	1,447,558
Total	2,551,996	511,581	80,621	3,144,198

[a]Vital Statistics of the United States.
National Center for Health Statistics, DHEW, Washington, D.C. 1975

[b]Unpublished data from above.

Table 4-21 is a comparison of cadmium exposures among sources obtained by multiplying the population exposed to each source by the concentrations resulting from that source. Also, Table 4-22 describes the numbers of individuals exposed, within a given source category, as a function of annual concentration, from >0.1 ng Cd/m^3 to >10 ng/m^3. These air-level categories are broken down into two types: populations exposed to higher-than-specified concentrations and populations exposed from at least one point source within each category. In addition, Figure 4-6 depicts the states included in the census regions employed in Table 4-23, a tabulation of regional populations exposed to cadmium levels exceeding 0.1 nanograms Cd/m^3.

As noted earlier, smokers constitute a definite population at increased risk for adverse health effects of cadmium. Recent data from the National Clearinghouse for Smoking and Health (1975) provide a quantitative picture of the numbers of individuals as a function of age and sex who are smokers in the United States. Among adults over 20 years of age, 34 percent are smokers (46.9 million people) of whom 25.9 million are males. Average cigarettes consumed daily by men and women are 23 and 19 cigarettes daily. Of teenagers (13-19 years old), there are 6 million smokers, with increases in this number presently being seen. Thus, a very large segment of the present U.S. population can be expected to be at increased risk for adverse health effects of cadmium.

Also of special interest are the numbers of children in various urban areas who may be at increased risk to cadmium exposure, and Table 4-24 presents natality data for 1970 and 1975 as provided by the National

Center for Health Statistics (1975, 1978). As noted earlier, children are clearly at risk for increased absorption, but it is not necessarily the case that they are at special risk for experiencing health effects resulting from any short-term exposure or accumulation of cadmium. However, adverse health effects of cadmium vis-a-vis the population at large typically appear only after many years of low-level chronic exposure. Thus, an argument can be advanced that the segment of the present U.S. population that can most benefit from controlled environmental exposure to cadmium and its associated health effects are the very young. Conversely, it can also be argued that any substantial increases in general cadmium exposure, due to uncontrolled emissions into the environment from whatever source(s) in the future, would perhaps impact most heavily on the present U.S. pediatric population by virtue of sufficient time remaining in their lifespans for cadmium to ultimately accumulate to toxic levels.

4.7 REFERENCES FOR CHAPTER 4

Akland, G. G. Air Quality Data/Metals, 1970-1974, from National Air Surveillance Networks. EPA-600/4-76-041, U.S. Environmental Protection Agency, Research Triangle Park, N.C., 1976.

Andersson, A. On the influence of manure and fertilizers on the distribution and amounts of plant-available Cd in soils. Swed. J. Agric. Res. 6:27-36, 1976.

Berry, W.L., and A. Wallace. Trace Elements in the Environment - Their Role and Potential Toxicity as Related to Fossil Fuels - A Preliminary Study. UCLA, Los Angeles, CA, 1974.

Bogden, J. D., N. P. Singh, and M. M. Joselow. Cadmium, lead and zinc concentrations in whole blood samples of children. Environ. Sci. Technol. 8:740-742, 1974.

Bond, R. G., Straub, C. P., and Prober, R. (eds.) Handbook of Environmental Control, Vol 1: Air Pollution. CRC Press, Cleveland, 1972.

Clapp et al. In: CAST (Council for Agricultural Science and Technology). Application of sewage sludge to cropland; appraisal of potential hazards of the heavy metals to plants and animals. CAST. Report No. 64, Iowa State University, Ames, IA, 1976.

Commission of the European Communities. Criteria (Dose/Effect Relationships) for Cadmium. Pergamon Press, New York, 1978.

Corneliussen, P. E. Pesticide residues in total diet sample (V). Pest. Monitor. J. 4:80-105, 1970.

Cvetkova, R. P. Materials on the study of the influence of cadmium compounds on the generative function. Gig. Tr. Prof. Zabol. 14:31, 1970.

Deane, L. G., D. A. Lynn, and N. F. Surprenant. Cadmium: Control Strategy Analysis. ECA Cong., Bedford, Mass. U.S. Environmental Protection Agency, 1976.

Delves, H. T., B. E. Clayton, and J. Bicknell. Concentrations of trace metals in the blood of children. Br. J. Prev. Soc. Med. 27:100-107, 1973.

Dowdy, R. J., and W. E. Larson. The availability of sludge borne metals to various vegetable crops. J. Environ. Qual. 4:278-282, 1975.

Duggan, R. E., and P. E. Corneliussen. Dietary intake of pesticide chemicals in the United States. June, 1968-April, 1970. Pestic. Monitor. J. 5:331, 1972.

Elinder, C.-G., T. Kjellström, L. Linnman, and G. Pershagen. Urinary excretion of cadmium and zinc among persons from Sweden. Environ. Res. 15:1978.

Faoro, R. B., and T. B. McMullen. National Trends in Trace Metals in Ambient Air, 1965-1974. EPA-450/1-77-003, U.S. Environmental Protection Agency, Research Triangle Park, N.C., 1977.

Fleischer, M., A. F. Sarofim, D. W. Fossett, P. Hammond, H. T. Shocklette, I. C. T. Nisbet, and S. Epstein. Environmental impact of cadmium: A review by the panel on hazardous trace substances. Environ. Health Persp. 7:253-323, 1974.

Food and Drug Administration. Compliance Program Evaluation, FY'74 Total Diet Studies (7320.08). U.S. Department of Health, Education, and Welfare, Food and Drug Administration, Bureau of Foods, Washington, D.C. January 21, 1977.

Friberg, L., M. Piscator, G. F. Nordberg, and T. Kjellström. Cadmium in the Environment. CRC Press, Cleveland, 1974.

Gowen, J. A., G. B. Wiersma, and H. Tai. Residues in soil: Mercury and 2, 4D levels in wheat and soils from sixteen states. 1969. Pestic. Monitor. J. 10:111-113, 1976.

Gross, S. B., D. W. Yeager, and M. S. Middendorf. Cadmium in liver, kidney, and hair of humans, fetal through old age. J. Toxicol. Environ. Health. 2:153-167, 1976.

International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man: cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on related anesthetics, Vol II, World Health Organization, Lyon, 1976. pp. 39-74.

Johnson, D. E., R. J. Prevost, J. B. Tillery, and R. E. Thomas. The Distribution of Cadmium and Other Metals in Human Tissue. Final Report, Contract No. 68021725. Prepared by Southwest Research Institute, San Antonio, Texas, for U.S. Environmental Protection Agency, Washington, D.C. 1977.

Kawai, K., and K. Fukuda. Pathological findings in experimental cadmium poisoning. In: Materials of the Research Meeting Concerning Cadmium Poisoning. Japanese Association of Public Health, Tokyo, March 16, 1974. pp. 29-30.

Kawai, K., K. Fukuda, and M. Kimura. Morphological alterations in experimental cadmium exposure with special reference to the onset of renal lesion. In: Effects and DoseResponse Relationships of Toxic Metals. G. F. Nordberg (ed.). Elsevier, Amsterdam, 1976. pp. 343-370.

Kazantzis, G. Some longterm effects of cadmium on the human kidney. In: Cadmium 77: Edited Proceedings, First International Cadmium Conference. Metal Bulletin Ltd., London, 1978. pp. 194-198.

Kjellström, T. A mathematical model for the accumulation of cadmium in human kidney cortex. Nord. Hyg. Tdskr. 53:111-119, 1971.

Kjellström, T. Epidemiological evaluation of proteinuria in long-term cadmium exposure with a discussion of dose-response relationships. In: Effects and Dose-Response Relationships of Heavy Metals. G. F. Nordberg (ed.), Elsevier, Amsterdam, 1976. pp. 309-330.

Kjellström, T. (ed.). Exposure and Accumulation of Cadmium in People from Japan, U.S.A. and Sweden. Report on a Three Year Cooperative Research Project. Environmental Protection Agency, Japan Society for Promotion of Science and Swedish National Environmental Board, June, 1978. Environ. Health Persp., in press.

Klein, D. H., and P. Russell. Heavy metals: Fallout around a power plant. Environ. Sci. Technol. 7:357-358, 1973.

Lauwerys, R. R., J. P. Bucket, H. A. Ralls, J. Brouwers, and D. Stanescu. Epidemiological survey of workers exposed to cadmium. Arch. Environ. Health. 28:145-148, 1974.

Lee, K. W., and D. R. Keeney. Cadmium and zinc additions to Wisconsin soils by commercial fertilizers and wastewater sludge application. Water Air Soil Pollut. 5:109-110, 1975.

Lucas, J. B., H. R. Pahren, J. A. Ryan, and G. K. Dotson. The impact of metals present in municipal sludges upon the human food chain - A risk assessment. In: Risk Assessment and Health Effects of Land Application

of Municipal Wastewater and Sludges, B. P.-Sagik and C. A. Sorber (eds.), Center for Applied Research and Technology, University of Texas at San Antonio, 1978. pp. 132-140.

MacLean, A. J. Cadmium in different plant species and its availability in soils as influenced by organic matter and additions of lime, P, Cd and Zn. Can. J. Soil Sci. 56:129-138, 1976.

Mahaffey, K. R., P. E. Corneliussen, C. F. Jelink, and J. A. Fioreno. Levels of trace contaminants in foods. In: Heavy Metals in the Environment - III, May 15-16, 1975. University of North Carolina, Chapel Hill. 13 p.

Miller, J. E., J. J. Hassett, and D. E. Koeppe. Uptake of cadmium by soybeans as influenced by soil cation exchange capacity, pH, and available phosphorus. J. Environ. Qual. 5(2):157-160, 1976.

Munshower, F. Cadmium compartmentation and cycling in a grass land ecosystem in the Deer Lodge Valley, Montana. University of Montana, Missoula, 1972.

National Center for Health Statistics, 1975.

National Center for Health Statistics, 1978.

National Clearinghouse for Smoking and Health, Atlanta, Georgia. 1975.

Natusch, D. F. S., J. R. Wallace, and C. A. Evans, Jr. Toxic trace elements: Preferential concentration in respirable particles. Science. 183:202-204, 1974.

Nogawa, K., A. Ishuzaki, S. Kawano. Statistical Observations of the Dose-Response Relationships of Cadmium Based on Epidemiological Studies in the Kakehashi River Basin. Environ. Res. 15:185-198, 1978.

Nomiyama, K. "Does a critical concentration in the human renal cortex exist?" J. Toxicol. Environ. Health. 3:607609, 1977.

Nomiyama, K. Studies concerning cadmium metabolism and the etiology of poisoning. Toxicol. Appl. Pharmacol. 31:412, 1975.

Nordberg, G. F. Models used for calculation of accumulation of toxic metals. Paper presented at 17th International Congress on Occupational Health. Buenos Aires, Argentina, Sept. 17-23, 1972.

Nordberg, G. F. Urinary, blood, and fecal cadmium concentrations as indices of exposure and accumulation. Paper presented at 17th International Congress on Occupational Health. Buenos Aires, Argentina, Sept. 17-23, 1972.

Nordberg, G. F. Health hazards of environmental cadmium pollution. Ambio 3:55-66, 1974.

Nordberg, G. F. (ed.). Effects and Dose-Response Relationships of Heavy Metals. Elsevier, Amsterdam, 1976.

Nordberg, G. F., and T. Norseth. Critical organ concepts and indicators of early effects in evaluating and establishing dose-response relationships for toxic metals. In: Effects and Dose-Response Relationships of Heavy Metals. G. F. Nordberg (ed.). Elsevier, Amsterdam, 1976. pp. 131-139.

Pfitzer, E. A. General concepts and definitions for dose-response and dose-effect relationship of toxic metals. In: Effects and Dose-Response Relationships of Heavy Metals. G. F. Nordberg (ed.). Elsevier, Amsterdam, 1976. pp. 140-146.

Pihl, R. O., and M. Parkes. Hair element content in learning disabled children. Science. 198:204-206, 1977.

Piscator, M. "Proteinuria data for group of workers in 1959 and 1977," cited in discussion of Tsuchiya, K. Criteria for health standards. In: Cadmium 77: Edited Proceedings, First International Cadmium Conference. Metal Bulletin Ltd., London, 1978. p. 247.

Reuss, J. O., H. L. Dooley, and W. Griffis. Uptake of cadmium from phosphate fertilizers by peas, radishes, and lettuce. J. Environ. Qual. 7(2):128-133, 1978.

Ryan, J. A. Cadmium: Utilization and Environmental Implication. In: Proceedings, First Annual Conference of Applied Research and Practice on Municipal and Industrial Waste. Madison, WI, 1978. pp. 269-285.

Sargent., D. H., and J. R. Metz. Technical and Microeconomic Analyses of Cadmium and Its Compounds. EPA 560/3-75-005, U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, D.C., 1975.

Schroeder, H. A., and J. J. Balassa. Cadmium: Uptake by vegetables from superphosphate and soil. Science. 140:819-820, 1963.

Shibko, S. I., and G. L. Braude. Cadmium in Food and Drinking Water - FDA Considerations. Department of Health, Education, and Welfare, Food and Drug Administration, Bureau of Foods, Washington, D.C.

Stenstrom, T., and M. Vahter. Cadmium and lead in Swedish commercial fertilizers. Ambio. 3(2):91-92, 1974.

Suzuki, Y. In: Proc. 47th General Assembly of Japan. Ind. Health Assoc. Nagowa. 1974. p. 124125.

Taylor, F. B. Trace elements and compounds in water. J. Am. Water Works. Assoc. 63:728-733, 1971.

Tsuchiya, K., Y. Seki, and M. Sugita. Biological threshold limits of lead and cadmium. Paper presented at the 17th International Congress on Occupational Health, Buenos Aires, Argentina, Sept. 17-23, 1972a.

Tsuchiya, K., Y. Seki, and M. Sugita. Organ and tissue cadmium concentrations of cadavers from accidental deaths. Paper presented at 17th International Congress on Occupational Health, Buenos Aires, Argentina, September 17-23, 1972b.

Tsuchiya, K., and M. Sugita. A mathematical model for deriving the biological half-life of a chemical. Nord. Hyg. Tdskr. 53:105, 1971.

U.S. Department of Health, Education and Welfare. 1970 Community Water Supply Study: Analyses of National Survey Findings. U.S. Dept. of Health, Education, and Welfare, U.S. Public Health Service, Washington, D.C., 1970.

U.S. Department of Health, Education and Welfare. Compliance Program Evaluation: FY 1974 Heavy Metals in Food Survey (Chemical Contaminants Project). U.S. Department of Health, Education, and Welfare, Washington, D.C., 1975.

U.S. Environmental Protection Agency. Air Quality Criteria document for Lead, EPA-600/8-77-017, GPO, Washington, D.C., 1977.

U.S. Environmental Protection Agency, Atmospheric Cadmium: Population Exposure Analysis (Draft). U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, N.C., 1978.

U.S. Environmental Protection Agency. Development Document for Effluent Limitations Guidelines and New Source Standards for the Basic Fertilizer Chemicals. EPA-440/1-74-011A, U.S. Environmental Protection Agency, Washington, D.C., 1974.

U.S. Environmental Protection Agency, Impact of Annual Cadmium Application Rates on Current Municipal Sludge Landspreading Practices. U.S. Environmental Protection Agency, Washington, D.C., 1978.

U.S. Environmental Protection Agency, Multimedia Levels Cadmium. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, D.C., 1977. EPA No. 560/6-77-032. p. 3-13.

U.S. Environmental Protection Agency. National Interim Primary Drinking Water Regulations, Part 141. Fed. Regist. 40:59566-59568, 1975.

U.S. Environmental Protection Agency. Solid waste disposal facilities: Proposed classification criteria. Fed. Regist. 43(25):Part II: 4942-4955, 1978.

U.S. Environmental Protection Agency. Sources of Atmospheric Cadmium. (Draft). U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, N.C., 1978.

Williams, C. H., and D. J. David. The effect of superphosphate on the cadmium content of soils and plants. Aust. J. Soil Res. 11(1):43-56, 1973.

Williams, C. H., and D. J. David. The accumulation in soil of cadmium residues from phosphate fertilizers and their effect on the cadmium content of plants. Soil Science 121(7):86-93, 1976.

World Health Organization. Environmental Health Criteria for Cadmium. Summary. WHO, Geneva. 1977.

Yost, K. J., M. D. Abel, G. J. Atchison, et al. The Environmental Flow of Cadmium and Other Trace Metals--Environmental Studies (Progress Report NSF Grant GI-35106). Purdue University, West Lafayette, Indiana, 1975.

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA-600/8-79-003	2.	3. RECIPIENT'S ACCESSION NO.
4. TITLE AND SUBTITLE Health Assessment Document for Cadmium		5. REPORT DATE January, 1979
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) L.D. Grant & W. Galke, ECAO, EPA, RTP,NC 27711; P. Mushak, UNC, Chapel Hill, NC 27514; A. Crocetti, NY Medical College, NY, NY 10029		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Environmental Criteria and Assessment Office, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711		10. PROGRAM ELEMENT NO. 1HA882
		11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

This document provides a critical assessment of health effects and public health risks associated with environmental exposure to cadmium (Cd). Sources and routes of exposure are discussed and identified. Dose-effect/response relationships and populations at special risk are delineated.

Cadmium is naturally present in most environmental media. Major anthropogenic sources are: (1) smelting and mining, (2) certain manufacturing processes, and (3) waste disposal operations. Food is the largest environmental source for most humans, although Cd intake from smoking can equal or exceed Cd intake from food.

Acute non-lethal exposure is associated with chronic respiratory effects. However, since most environmental exposures to Cd are of a long-term, low-level type, primary emphasis has been placed on discussing effects of such chronic exposure. Cadmium's accumulation in the kidney results in renal tubular dysfunction after many years of exposure. Estimates of the concentration of Cd in the renal cortex necessary to induce these effects and estimates of exposure necessary to produce the critical renal concentration vary widely, partially due to individual biological variability. Populations at special risk to Cd are cigarette smokers, as well as the older segments of the population (<50 years of age).

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS		b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Metals	Air Pollution	Cigarette Smoking	02A
Cadmium	Water Pollution	Pneumonitis	06A
Trace Elements	Food	Renal Tubular Dysfunction	06C
Smelting	Urological Diseases	Renal Cortex	06E
Mining	Nutritional Deficiencies	Phosphate Fertilizer	06F
Electroplating	Sludge	Body Burden	06H
Earth Fills	Public Health	Human Health	06P
Incinerators			13B

18. DISTRIBUTION STATEMENT RELEASE TO PUBLIC	19. SECURITY CLASS (This Report) UNCLASSIFIED	21. NO. OF PAGES
	20. SECURITY CLASS (This page)	22. PRICE

EPA Form 2220-1 (9-73)