TOXICOLOGICAL PROFILE FOR ZINC

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A Toxicological Profile for Zinc was released on December 1990. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The revised list of the 275 most hazardous substances was published in the Federal Register on October 28, 1992 (57 FR 48801). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); and October 17, 1991 (56 FR 52166).

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

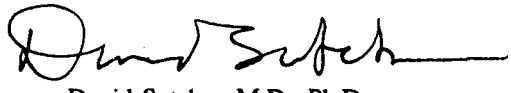
The ATSDR toxicological profile is intended to succinctly characterize the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented, but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, that describes in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protect public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Reviews. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for zinc. The panel consisted of the following members:

1. Dr. Martin Alexander, Professor, Soil Microbiology, Dept. of Soil, Crop, and Atmospheric Sciences, Cornell University, Ithaca, New York
2. Dr. Ernest Foulkes, Deputy Director, Department of Environmental Health, University of Cincinnati, College of Medicine, Cincinnati, Ohio
3. Dr. Ingeborg Harding-Barlow, Private Consultant, Palo Alto, California.

These experts collectively have knowledge of zinc's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about zinc and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,350 hazardous waste sites as the most serious in the nation. These sites comprise the "National Priorities List" (NPL): Those sites which are targeted for long-term federal cleanup activities. Zinc has been found in at least 776 of the sites on the NPL. However, the number of NPL sites evaluated for zinc is not known. As EPA evaluates more sites, the number of sites at which zinc is found may increase. This information is important because exposure to zinc may cause harmful health effects and because these sites are potential or actual sources of human exposure to zinc.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as zinc, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, gender, nutritional status, family traits, life-style, and state of health.

1.1 WHAT IS ZINC?

Zinc is one of the most common elements in the earth's crust. Zinc is found in the air, soil, and water and is present in all foods. In its pure elemental (or metallic) form, zinc is a bluish-white shiny metal. There is no information on the taste and odor of metallic

zinc. Powdered zinc is explosive and may burst into flames if stored in damp places. Metallic zinc has many uses in industry. A common use is as coating for iron or other metals so that they do not rust or corrode. Metallic zinc is also mixed with other metals to form alloys such as brass and bronze. A zinc and copper alloy is used to make pennies in the United States. Metallic zinc is also used to make dry cell batteries.

Zinc can also combine with other elements, such as chlorine, oxygen, and sulfur, to form zinc compounds. Zinc compounds that may be found at hazardous waste sites are zinc chloride, zinc oxide, zinc sulfate, and zinc sulfide. This profile focuses primarily on metallic zinc and commonly found or used zinc compounds. Most zinc ore found naturally in the environment is in the form of zinc sulfide. Zinc compounds are widely used in industry. Zinc compounds are not explosive or flammable. Zinc sulfide is gray-white or yellow-white, and zinc oxide is white. Both of these compounds are used to make white paints, ceramics, and several other products. Zinc oxide is also used in producing rubber. Zinc compounds, such as zinc acetate, zinc chloride, and zinc sulfate, are used in preserving wood and in manufacturing and dyeing fabrics. Zinc chloride is also the major ingredient in smoke from smoke bombs. Zinc compounds are also used by the drug industry as ingredients in some common products, such as sun blocks, diaper rash ointments, deodorants, athlete's foot preparations, acne and poison ivy preparations, and antidandruff shampoos.

Zinc is an essential food element needed by the body in small amounts. Too little zinc in the diet can lead to poor health, reproductive problems, and lowered ability to resist disease. Too much zinc can also be harmful to health. More information can be found on the chemical and physical properties of zinc in Chapter 3 and on its occurrence and fate in the environment in Chapter 5.

1.2 WHAT HAPPENS TO ZINC WHEN IT ENTERS THE ENVIRONMENT?

Zinc enters the air, water, and soil as a result of both natural processes and human activities. Most zinc enters the environment as the result of human activities, such as

mining, purifying of zinc, lead, and cadmium ores, steel production, coal burning, and burning of wastes. These releases can increase zinc levels in the atmosphere. Waste streams from zinc and other metal manufacturing and zinc chemical industries, domestic waste water, and run-off from soil containing zinc can discharge zinc into waterways. The level of zinc in soil increases mainly from disposal of zinc wastes from metal manufacturing industries and coal ash from electric utilities. In air, zinc is present mostly as fine dust particles. This dust eventually settles over land and water. Rain and snow aid in removing zinc from air. Most of the zinc in bodies of water, such as lakes or rivers, settles on the bottom. However, a small amount may remain either dissolved in water or as fine suspended particles. The level of dissolved zinc in water may increase as the acidity of water increases. Some fish can collect zinc in their bodies if they live in water containing zinc. Most of the zinc in soil is bound to the soil and does not dissolve in water. However, depending on the characteristics of the soil, some zinc may reach groundwater. Contamination of groundwater from hazardous waste sites has been noticed. Zinc may be taken up by animals eating soil or drinking water containing zinc. If other animals eat these animals, they will also have increased amounts of zinc in their bodies. For more information about what happens to zinc in the environment, see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO ZINC?

We are exposed to small amounts of zinc compounds in food every day. The average daily zinc intake through the diet in this country ranges from 7 to 16.3 milligrams (mg). Food may contain levels of zinc ranging from approximately 2 parts of zinc per million (ppm) parts of foods (e.g., leafy vegetables) to 29 ppm (meats, fish, poultry). Zinc is also present in most drinking water. Drinking water or other beverages may contain high levels of zinc if they are stored in metal containers or flow through pipes that have been coated with zinc to resist rust. Drinking water may also be contaminated by zinc from industrial sources or toxic waste sites. High-level exposure to zinc may also result from taking too many zinc dietary supplements. Fetuses and nursing children may be exposed to the zinc in the blood or milk of their mothers.

In general, levels of zinc in air are relatively low and fairly constant. Average levels of zinc in the air throughout the United States are less than 1 microgram of zinc per cubic meter ($\mu g/m^3$) of air, but range from 0.1 to 1.7 $\mu g/m^3$ in areas near cities. Air near industrial areas may have higher levels of zinc. The average zinc concentration for a l-year period was 5 $\mu g/m^3$ in one area near an industrial source.

About 150,000 workers are exposed to zinc at their jobs. Jobs where people are exposed to zinc include zinc mining, smelting, and welding; manufacture of brass, bronze, or other zinc-containing alloys; manufacture of galvanized metals; and manufacture of machine parts, rubber, paint, linoleum, oilcloths, batteries, some kinds of glass and ceramics, and dyes. People at construction jobs, automobile mechanics, and painters are also exposed to zinc.

For more information on exposure to zinc, see Chapter 5.

1.4 HOW CAN ZINC ENTER AND LEAVE MY BODY?

Zinc can enter the body through the digestive tract if you eat food or drink water containing it. Zinc can also enter through your lungs if you inhale zinc dust or fumes from zinc-smelting or zinc-welding operations on your job. The amount of zinc that passes directly through the skin is relatively small. The most likely route of exposure near NPL waste sites is through drinking water containing a high amount of zinc. Zinc is stored throughout the body. Zinc increases in blood and bone most rapidly after exposure. Zinc may stay in the bone for many days after exposure. Normally, zinc leaves the body in urine and feces. More information on how zinc enters and leaves your body can be found in Chapter 2.

1.5 HOW CAN ZINC AFFECT MY HEALTH?

Inhaling large amounts of zinc (as zinc dust or fumes from smelting or welding) can cause a specific short-term disease called metal fume fever. However, very little is known about the long-term effects of breathing zinc dust or fumes.

Taking too much zinc into the body through food, water, or dietary supplements can also affect health. The levels of zinc that produce adverse health effects are much higher than the Recommended Dietary Allowances (RDAs) for zinc of 15 mg/day for men and 12 mg/day for women. If large doses of zinc (10-15 times higher than the RDA) are taken by mouth even for a short time, stomach cramps, nausea, and vomiting may occur. Ingesting high levels of zinc for several months may cause anemia, damage the pancreas, and decrease levels of highdensity lipoprotein (HDL) cholesterol. We do not know if high levels of zinc affect the ability of people to have babies or cause birth defects in humans.

Eating food containing very large amounts of zinc (1,000 times higher than the RDA) for several months caused many health effects in rats, mice, and ferrets, including anemia and injury to the pancreas and kidney. Rats that ate very large amounts of zinc became infertile. Rats that ate very large amounts of zinc after becoming pregnant had smaller babies. Putting low levels of certain zinc compounds, such as zinc acetate and zinc chloride, on the skin of rabbits, guinea pigs, and mice caused skin irritation. Skin irritation from exposure to these chemicals would probably occur in humans. EPA has determined that zinc is not classifiable as to its human carcinogenicity.

Consuming too little zinc is at least as important a health problem as consuming too much zinc. Without enough zinc in the diet, people may experience loss of appetite, decreased sense of taste and smell, decreased immune function, slow wound healing, and skin sores. Too little zinc in the diet may also cause poorly developed sex organs and retarded growth in young men. If a pregnant woman does not get enough zinc, her babies may have growth retardation.

More information on the health effects linked with exposure to higher than normal levels of zinc is presented in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ZINC?

A medical test exists that can determine whether your body fluids contain high levels of zinc. Samples of blood or feces can be collected in a doctor's office and sent to a laboratory that can measure zinc levels. It is easier for most laboratories to measure zinc in blood than in feces. The presence of high levels of zinc in the feces can mean recent high zinc exposure. High levels of zinc in the blood can mean high zinc consumption and/or high exposure. High zinc levels in blood or feces reflect the level of exposure to zinc. Measuring zinc levels in additional fluids (e.g., urine and saliva) would probably provide more information about zinc exposure. Tests to measure zinc in hair may provide information on long-term zinc exposure. However, no quantitative correlation has been found between hair zinc levels and zinc exposure. These tests are not routinely used. More information on tests to measure zinc in the body can be found in Chapter 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has set standards and guidelines to protect individuals from the potential health effects of excessive zinc. EPA has stated that drinking water should contain no more than 5 mg of zinc per liter of water (5 mg/L, or 5 ppm) because of taste. Furthermore, any release of more than 1,000 pounds (or in some cases 5,000 pounds) of zinc or its compounds into the environment (i.e., water, soil, or air) must be reported to EPA.

The National Academy of Sciences (NAS) estimates an RDA for zinc of 15 mg/day (men). Fifteen mg/day is the same as 0.21 mg per kilogram (kg) of body weight per day for an average adult male (70 kg). An RDA of 12 mg/day was established for women

because they usually weigh less than men. Lower zinc intake was recommended for infants (5 mg/day) and children (10 mg/day) because of their lower average body weights. The RDA provides a level of adequate nutritional status for almost the entire population. Extra dietary levels of zinc are recommended for women during pregnancy and lactation. An RDA of 15 mg/day was set for pregnant women. Women who nurse their babies need 19 mg/day during the first 6 months and 16 mg/day during the second 6 months of nursing.

To protect workers, the Occupational Safety and Health Administration (OSHA) has set a legal limit of 1 mg/m^3 for zinc chloride in workroom air. This regulation means that the workroom air should contain no more than an average of 1 mg/m^3 of zinc chloride over an 8-hour working shift of a 40-hour workweek. The National Institute for Occupational Safety and Health (NIOSH) recommends that the level of zinc oxide in workplace air should not exceed an average of 5 mg/m^3 over a lo-hour period of a 40-hour work week. For more information on recommendations and standards for zinc exposure, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry

Division of Toxicology

1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances,

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of zinc. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Zinc is an essential nutrient in humans and animals that is necessary for the function of a large number of metalloenzymes. These enzymes include alcohol dehydrogenase, alkaline phosphatase, carbonic anhydrase, leucine aminopeptidase, super-oxide dismutase, and deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) polymerase. As such, zinc is required for normal nucleic acid, protein, and membrane metabolism, as well as cell growth and division. Zinc also plays an essential role in the maintenance of nucleic acid structure of genes (zinc finger phenomenon). Zinc deficiency has been associated with dermatitis, anorexia, growth retardation, poor wound healing, hypogonadism with impaired reproductive capacity, impaired immune function, and depressed mental function; an increased incidence of congenital malformations in infants has also been associated with zinc deficiency in the mothers (Cotran et al. 1989; Elinder 1986; Sandstead 1981). Therefore, certain levels of zinc intake are recommended. The RDA for zinc is 15 mg/day in men and 12 mg/day in women (NAS/NRC 1989b). Higher RDAs are recommended for women during pregnancy and lactation (15 mg/day for pregnant women, 19 mg/day for nursing women during the first 6 months, and 16 mg/day during the second 6 months of nursing).

Just as zinc deficiency has been associated with adverse effects in humans and animals, overexposures to zinc also have been associated with toxic effects. This chapter contains a description of the toxic effects that have been associated with exposures to high levels of zinc and selected zinc compounds by the inhalation, oral, and dermal routes. Specifically, zinc chloride, zinc oxide, zinc sulfate, and zinc sulfide will be considered. Other zinc compounds are discussed in this chapter whenever data regarding these compounds add relevant information to the

discussion on zinc. Any general comments regarding the lack of data on zinc refer to both zinc and its compounds.

Because there are differences in toxicity between the various zinc compounds following inhalation exposure, these compounds will be discussed under separate subheadings in Section 2.2.1 (Inhalation Exposure). After oral or dermal exposure, the toxicities are comparable for all zinc compounds. Therefore, in Section 2.2.2 (Oral Exposure) and Section 2.23 (Dermal Exposure), the discussion will not be subdivided, but the specific zinc compounds will be identified in each case.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure - inhalation, oral, and dermal; and then by health effect - death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods - acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure (LSE) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects

is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the LSE tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

2.2.1 Inhalation Exposure

2.2.1.l Death

In humans, death has resulted from acute exposure to zinc compounds. When a high concentration (estimated at 33,000 mg zinc/m^3) of zinc chloride smoke resulted from the explosion of many generators in a tunnel following a bombing raid in World War II, 10 of the 70 exposed people in the tunnel died within 4 days (Evans 1945). The smoke generated contained mainly zinc chloride, but exposure to other constituents, namely zinc oxide, hexachloroethane, calcium silicate, and an igniter, was also possible. Therefore, the deaths resulting from the explosion cannot be conclusively attributed to exposure to zinc chloride only. This is the only human study reporting an estimated exposure level that caused death. Hence, this level is reported as a LOAEL in Table 2-l and Figure 2-1. Another study reported the death of a fireman exposed to the contents of a smoke bomb in a closed environment (Milliken et al. 1963). The man died 18 days after exposure because of respiratory difficulty. Again, exposure to zinc chloride was simultaneous with exposure to other substances in the smoke. Two soldiers exposed without gas masks to zinc chloride smoke during military training developed severe adult respiratory distress syndrome (ARDS) and died 25-32 days after the incident (Hjortso et al. 1988). Diffuse microvascular obliteration, widespread occlusion of the pulmonary arteries, and extensive interstitial and intra-alveolar fibrosis were observed at autopsy. Zinc levels in major

TABLE 2-1. Levels of Significant Exposure to Zinc - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL ($mg\ Zn/m^3$)	LOAEL (effect) Less serious ($mg\ Zn/m^3$)	LOAEL (effect) Serious ($mg\ Zn/m^3$)	Reference	Form
ACUTE EXPOSURE								
Death								
1	Human	<1 hr				33000 (10/70 died)	Evans 1945	chloride
Systemic								
2	Human	2 hr	Resp	.0036			Linn et al. 1981	amm sulfate
3	Human	1 d 2hr/d	Resp		3.9 (dyspnea, increased airway resistance)		Gordon et al. 1992	oxide
			Other		3.9 (fever/chills)			
4	Human	15-30 min	Resp		77 (minimal change in pulmonary function)		Blanc et al. 1991	oxide
5	Human	6-8 hr (occup)	Resp	0.034			Marquart et al. 1989	oxide
6	Human	10.5-12 min	Resp		600 (decreased vital capacity)		Sturgis et al. 1927	oxide
			Gastro		600 (nausea)			
			Hemato		600 (increased leukocytes)			
7	Rat	1 d 3hr/d	Resp		2.2 (increased LDH protein in broncho-alveolar lavage fluid)		Gordon et al. 1992	oxide
8	Rabbit	1 d 2hr/d	Resp	4.6			Gordon et al. 1992	oxide
9	Gn pig	1-3 d 3hr/d	Resp	1.8	4.7 (increased neutrophils, LDH, and protein in broncho-alveolar lavage fluid)		Conner et al. 1988	oxide

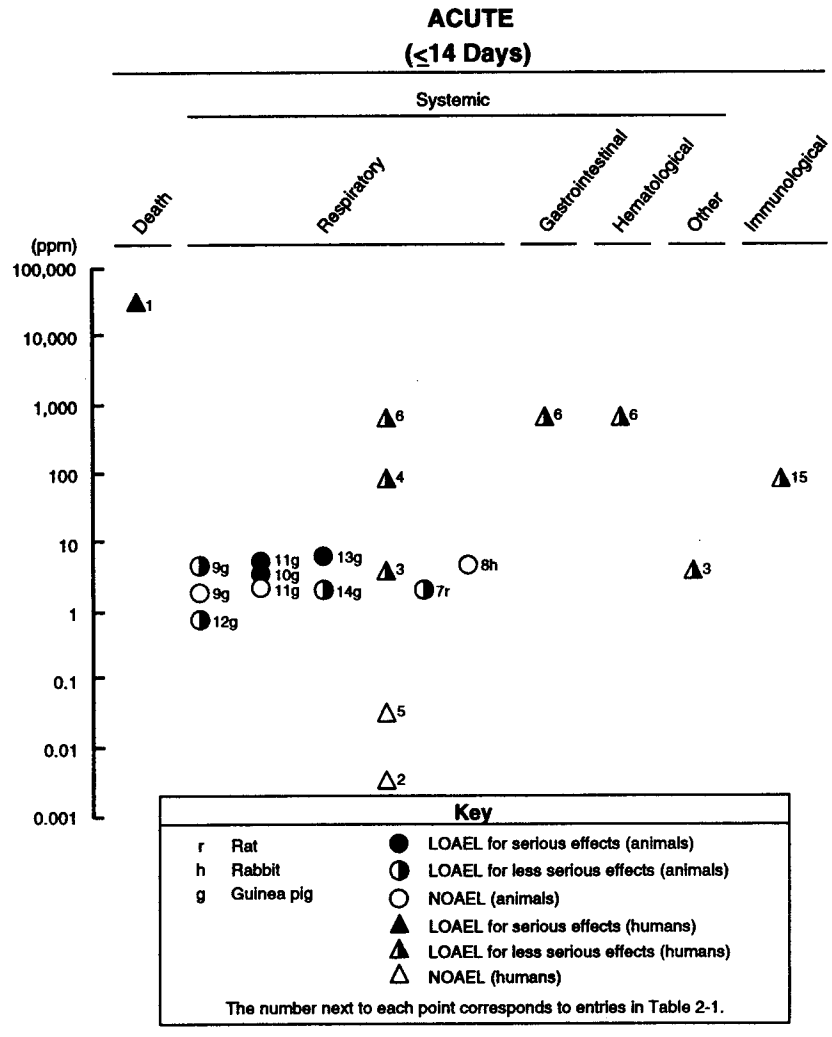
TABLE 2-1. Levels of Significant Exposure to Zinc - Inhalation (continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL ($mg\ Zn/m^3$)	LOAEL (effect) Less serious ($mg\ Zn/m^3$)	LOAEL (effect) Serious ($mg\ Zn/m^3$)	Reference	Form
10	Gn pig	6 d 3hr/d	Resp			3.7 (impaired lung function; inflammation; increased pulmonary resistance; increased lung weight)	Lam et al. 1985	oxide
11	Gn pig	5 d 3hr/d	Resp	2.2		5.6 (impaired lung function; increased lung weight)	Lam et al. 1988	oxide
12	Gn pig	1 hr	Resp		0.73 (decreased compliance)		Amdur et al. 1982	oxide
13	Gn pig	3 hr	Resp			6.3 (decreased functional residual capacity)	Lam et al. 1982	oxide
14	Gn pig	1 d 3hr/d	Resp		2.2 (increased LDH and protein in bronchoalveolar lavage fluid)		Gordon et al. 1992	oxide
Immunological								
15	Human	15-30 min			77 (increased number of leukocytes, T cells, T suppressor cells, and natural killer cells in bronchoalveolar lavage fluid)		Blanc et al. 1991	oxide

[a]The number corresponds to entries in Figure 2-1.

amm sulfate = ammonium sulfate; chloride = zinc chloride; d = day(s); Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level; (occup) = occupational; oxide = zinc oxide; Resp = respiratory; Zn = zinc

FIGURE 2-1. Levels of Significant Exposure to Zinc - Inhalation



organs and tissues obtained during autopsy were within the normal range, and no zinc particles were observed by scanning electron microscopy. According to the authors, the fumes from the smoke bombs consisted mainly of zinc chloride. However, no exposure levels were estimated, and other substances were also present in the smoke.

A case study presented by Murray (1926) reported on an infant death due to bronchopneumonia resulting from inhalation, and possibly ingestion of an unspecified amount of zinc stearate powder spilled from a container. However, it is unclear whether the death was due to the zinc content or whether aspiration bronchopneumonia would result from inhalation of similar powders that do not contain zinc.

In mice, the reported LCT_{50}, (product of lethal concentration and time to kill 50% of animals) of zinc chloride is 11,800 mg-min/m^3 (Schenker et al. 1981). However, Schenker et al. (1981) did not provide information on how this value was determined. Following exposure to zinc chloride smoke for 3-20 weeks, mortality was 50% in mice exposed to 121.7 mg zinc/m^3 (compared to 20% in controls) and 22% in guinea pigs exposed to 119.3 mg zinc/m^3 (compared to 8% in controls) (Marrs et al. 1988). The smoke was similar to that described by Evans (1945) and also contained zinc oxide, hexachloroethane, and other compounds.

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to zinc or zinc compounds. The systemic effects observed after inhalation exposure are discussed below. In most cases, the effects of zinc are discussed without separating effects caused by the individual zinc compounds. However, the respiratory effects of the individual zinc compounds are discussed separately because the nature of the respiratory toxicity differs depending on the particular compound to which one is exposed. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects

Zinc Oxide. Metal fume fever, a well-documented acute disease induced by intense inhalation of metal oxides, especially zinc, temporarily impairs pulmonary function but does not progress to chronic lung disease (Brown 1988; Drinker et al. 1927b; Malo et al. 1990). Symptoms generally appear within a few hours after acute exposure, usually with dryness of the throat and coughing (Drinker and Drinker 1927b). The most prominent respiratory effects of metal fume fever are substernal chest pain, cough, and dyspnea (Rohrs 1957). The impairment of pulmonary function is characterized by reduced lung volumes and a decreased diffusing capacity of carbon monoxide (Malo et al. 1990; Vogelmeier et al. 1987). The respiratory effects have been shown to be accompanied by an increase in bronchiolar leukocytes (Vogelmeier et al. 1987). The respiratory symptoms generally disappear in the exposed individual within l-4 days (Brown 1988; Drinker et al. 1927b; Sturgis et al. 1927). Refer to the Other Systemic Effects section below for further details on nonrespiratory effects related to metal fume fever. Inhalation of zinc oxide is most likely to occur in occupational situations where zinc smelting or welding take place. Ultrafine zinc oxide particles (0.2-1.0 pm) originate from heating zinc beyond its boiling point in an oxidizing atmosphere. Upon inhalation, these small particles (< 1 pm) reach the alveoli and cause inflammation and tissue damage in the lung periphery (Brown 1988; Drinker et al. 1927b; Vogelmeier et al. 1987).

A number of studies have measured exposure levels associated with metal fume fever. Workers involved in pouring molten zinc reported shortness of breath and chest pains 2-12 hours following exposure to 320-580 mg zinc/m^3 as zinc oxide for l-3 hours (Hammond 1944); the number of workers was not reported. Two volunteers had nasal passage irritation, cough, substernal chest pain, persistent rales of the lung base, and a decreased vital capacity for approximately 3-49 hours following acute inhalation (10-12 minutes) of 600 mg zinc/m^3 as zinc oxide (Sturgis et al. 1927). A subject experimentally exposed to zinc oxide fumes reported mild pain when breathing deeply the next day after a 5-hour exposure to 430 mg zinc/m^3 (Drinker et al. 1927a). Minimal changes in forced expiratory flow were observed 1 hour after a 15-30-minute exposure to 77 mg zinc/m3 as zinc oxide (Blanc et al. 1991).

Acute experimental exposures to lower concentrations of zinc oxide (14 mg/m^3 for 8 hours or 45 mg zinc/m^3 for 20 minutes) and occupational exposures to similar concentrations (8-12 mg

zinc/m^3 for 1-3 hours and 0.034 mg zinc/m^3 for 6-8 hours) have not produced symptoms of metal fume fever (Drinker et al. 1927b; Hammond 1944; Marquart et al. 1989). In a single-blind experiment, exposure of subjects to 3.9 mg zinc/m3 as zinc oxide resulted in sore throat and chest tightness but no impairment of pulmonary function (Gordon et al. 1992). It is speculated that subjects in other studies may have been less susceptible because of the development of tolerance to zinc (Gordon et al. 1992). Recurrent episodes of cough and dyspnea were reported in a former mild smoker 3 years after beginning work in a metal foundry where exposure to zinc oxide presumably occurred (Ameille et al. 1992). This case was distinguishable from metal fume fever because of the lack of tolerance to zinc (as shown by the late emergence of symptoms).

Several animal studies have been conducted to quantitate specific effects after acute zinc oxide inhalation. As in human exposure, the respiratory system is the primary site of injury following inhalation exposure. Acute administration of 88-482 mg zinc/m^3 as zinc oxide to rats and rabbits resulted in the following pulmonary changes: grayish areas with pulmonaty congestion, various degrees of peribronchial leukocytic infiltration, and exudate composed almost entirely of polymorphonuclear leukocytes in bronchi (Drinker and Drinker 1928). A minimum effect level could not be determined because the concentration varied widely during exposure. Cats similarly exposed exhibited more severe effects including bronchopneumonia, leukocyte infiltration into alveoli, and grayish areas with congestion. During the exposure period, the cats demonstrated labored breathing and evidence of upper respiratory tract obstruction.

Guinea pigs administered 0.73 mg zinc/m^3 as zinc oxide for 1 hour had a progressive decrease in lung compliance but no change in air flow resistance. These observations reflect a response in the lung periphery where submicrometer aerosols are likely to deposit (Amdur et al. 1982). The authors postulated that reduced compliance may be associated with human metal fume fever.

In contrast to the results of Amdur et al. (1982), no effects on ventilation, lung mechanics (respiratory frequency, tidal volume, pulmonary resistance, and pulmonary compliance), diffusing capacity of carbon monoxide, or most lung volume parameters were observed by Lam et al. (1982) following the exposure of guinea pigs to 6.3 mg zinc/m^3 as zinc oxide for 3 hours. However, functional residual capacity was significantly decreased. The discrepancy between the results of Amdur et al. (1982) and Lam et al. (1982) may be attributable to the use of anesthetized animals by Lam et al. (1982). In a later study, exposures of guinea pigs to 3.7 or 4.3 mg zinc/m^3 as zinc

oxide for 3 hours/day, for 6 days, resulted in transient functional, morphological, and biochemical changes (Lam et al. 1985). Functional changes included increased flow resistance, decreased lung compliance, and decreased diffusing capacity, all of which returned to normal within 24-72 hours following exposure. The morphological changes (increased lung weight, inflammation involving the proximal portion of alveolar ducts and adjacent alveoli, interstitial thickening, and increased pulmonary macrophages and neutrophils in adjacent air spaces) were, however, still present at 72 hours. In guinea pigs with evidence of an inflammatory reaction involving the peripheral airways, DNA synthesis increased in bronchiolar cells. Similarly, exposure of guinea pigs to 5.6 mg zinc/m^3 as zinc oxide for 3 hours/day, for 5 days, resulted in gradual decreases in total lung capacity, vital capacity, and decreased carbon monoxide diffusing capacity (Lam et al. 1988); however, no effects were observed in guinea pigs exposed to 2.2 mg zinc/m^3. The reason that effects have been seen in the guinea pig at exposure levels lower than humans may have to do with the structural features of the guinea pig lung. The bronchi and peripheral airways of guinea pigs have a thicker smooth muscle layer and only a small surface area covered by alveolar sacs compared to the bronchi and peripheral airways of other laboratory animals and humans. This makes the guinea pig more susceptible than other laboratory animals to functional impairment of the peripheral airways and should be noted in toxicity comparisons (Lam et al. 1982).

The bronchoalveolar lavage fluid of rats or guinea pigs exposed to 2.2 mg zinc/m^3 for 3 hours contained increased levels of lactate dehydrogenase and protein, suggesting effects on cell viability or membrane permeability (Gordon et al. 1992). Rabbits were not affected following a similar exposure to 4.6 mg zinc/m^3 for 2 hours. Guinea pigs had foci of inflammation after exposure to 4.7 mg zinc/m^3 for 3 days, and the bronchoalveolar lavage fluid contained increased levels of protein, angiotensin converting enzyme, and neutrophils (Conner et al. 1988).

Zinc Chloride. Zinc chloride, a corrosive inorganic salt, is more damaging than zinc oxide to the mucous membranes of the nasopharynx and respiratory tract upon contact. Zinc chloride is a primary ingredient in smoke bombs used by the military for screening purposes, crowd dispersal, and occasionally in military and civilian fire-fighting exercises. Reports of serious respiratory injury have been reported to result from accidental inhalation of smoke from these bombs. These reports are of limited use in assessing the toxicity of zinc chloride because exposure to other compounds, usually hexachloroethane, zinc oxide, and calcium silicides, also occur. Furthermore, the specific concentrations inhaled are usually unknown. Despite these limitations, several case

studies have described similar respiratory effects in humans following acute inhalation exposures. These effects include dyspnea, cough, pleuritic chest pain, bilateral diffuse infiltrations, pneumothorax, and acute pneumonitis from respiratory tract irritation (Johnson and Stonehill 1961; Matarese and Matthews 1966; Schenker et al. 1981). In the study by Johnson and Stonehill (1961) cough, dyspnea, burning throat, diffuse infiltrates throughout the lung, chemical pneumonitis, and decreased vital capacity were observed at an estimated zinc chloride exposure level of 4,075 mg/m^3 (1,955 mg zinc/m^3). In other studies, more severe effects have occurred, including ulcerative and edematous changes in mucous membranes, fibrosis, subpleural hemorrhage, advanced pulmonary fibrosis, and fatal respiratory distress syndrome (Evans 1945; Hjortso et al. 1988; Homma et al. 1992; Milliken et al. 1963).

Focal alveolitis, consolidation, emphysema, infiltration with macrophages, and fibrosis were observed in guinea pigs that died following exposure to 119 mg zinc/m^3 as zinc chloride smoke for 1 hour/day, 5 days/week, for up to 3 weeks (Marrs et al. 1988). Thirteen months after a 20-week exposure, rats and mice inhaling 121.7 mg zinc/m^3 as zinc chloride smoke for 1 hour/day, 5 days/week, showed increased macrophages in the lungs (Marrs et al. 1988). The smoke also contained zinc oxide, hexachloroethane, and other compounds.

Zinc Ammonium Sulfate. Zinc ammonium sulfate is a compound emitted during combustion of fossil fuels and is, therefore, found in the ambient air. Humans acutely exposed to a concentration of 0.0036 mg zinc/m^3 as zinc ammonium sulfate for 2 hours exhibited minimal or no short-term respiratory effects (Linn et al. 1981). However, most human exposures to an ambient air pollutant such as zinc ammonium sulfate are chronic, and this study provides little information about the health effects associated with typical exposures.

No studies were located regarding respiratory effects in animals after inhalation exposure to zinc ammonium sulfate.

Zinc Stearute. Inhalation of zinc stearate powder resulted in aspiration bronchopneumonia in an infant (Murray 1926). However, it is unclear whether the bronchopneumonia resulted from the inhalation of zinc stearate powder specifically or from the inhalation of powders in general.

2. HEALTH EFFECTS

No studies were located regarding respiratory effects in animals after inhalation exposure to zinc stearate.

Cardiovascular Effects. No atypical heart sounds or blood pressure abnormalities were observed in 24 employees occupationally exposed to concentrations as high as 130 mg zinc/m^3 of metallic zinc dust, zinc oxide dust, zinc sulfide dust, or lithophone dust (a combination of barium sulphate and ≈30% zinc sulphide) for 2-35.5 years (Batchelor et al. 1926). However, this study is limited because only selected employees were examined, and they were not compared to controls.

Extremely limited information was located regarding cardiovascular effects in animals following inhalation exposure to zinc. Routine gross and microscopic examination of the hearts of rats and mice revealed no adverse effects 13 months after exposure to 121.7 mg zinc/m^3 as zinc chloride smoke (also containing other compounds) for 1 hour/day, 5 days/week, for 20 weeks (Marrs et al. 1988). Similarly, no changes were observed in the hearts of guinea pigs exposed to 119.3 mg zinc/m^3 as zinc chloride smoke for 1 hour/day, 5 days/week, for 3 weeks, and then observed for an additional 17 months (Marrs et al. 1988).

Gastrointestinal Effects. Nausea was reported by humans exposed to high concentrations of zinc oxide fumes (Hammond 1944; Rohrs 1957; Sturgis et al. 1927) and zinc chloride smoke (Evans 1945; Johnson and Stonehill 1961; Schenker et al. 1981). The zinc chloride smoke also contained zinc oxide, hexachloroethane, and other compounds. In general, exposure levels associated with nausea have not been reported. However, exposures to 320 mg zinc/m^3 as zinc oxide for l-3 hours (Hammond 1944) or 600 mg zinc/m^3 as zinc oxide for lo-12 minutes (Sturgis et al. 1927) were both reported to have resulted in nausea. Autopsies of victims who died following exposure to very high concentrations of zinc chloride smoke revealed irritation of the stomach and intestines (Evans 1945). The smoke also contained zinc oxide, hexachloroethane, and other compounds. Workers in the galvanizing industry were found by McCord et al. (1926) to have a higher than expected incidence of gastrointestinal problems; however, these individuals may have been exposed to other chemicals (arsenic, hydrogen sulfide). Of 15 workers examined with 7-20 years of experience, 12 had frequent episodes of epigastric or abdominal pain, nausea, vomiting, ulcers, constipation, tarry stools, and/or gas. It is unclear whether these effects were due to systemic zinc or were the result of direct contact with the gastrointestinal tract following mucociliary clearance of inhaled zinc particles and subsequent swallowing. In contrast, 24 workers

with 2-35.5 years of exposure to ≤130 mg zinc/m^3 as metallic zinc dust, zinc sulfide dust, zinc oxide, or lithophone dust reported no nausea or vomiting and only occasional mild abdominal discomfort that could not be attributed with certainty to zinc exposure (Batchelor et al. 1926). A study examining the acidity of the stomach contents after stimulation in controls and workers employed in the production of brass alloys showed that stomach acidity was similar in the two groups prior to stimulation but remained elevated for longer periods after stimulation in the exposed workers (Hamdi 1969). This was proposed to account for the gastric complaints of workers exposed to zinc fumes. Despite these findings, X-rays showed no lesions in the stomachs or duodenums of exposed workers.

The only information available regarding gastrointestinal effects in animals was found in a study by Marrs et al. (1988) in which rats and mice were exposed to 121.7 mg zinc/m^3 as zinc chloride smoke (which also contains zinc oxide, hexachlorophene, and other compounds) for 1 hour/day, 5 days/week, for 20 weeks, and then observed for an additional 13 months. In the same study, guinea pigs were exposed to 119.3 mg zinc/m^3 as zinc chloride smoke for 1 hour/day, 5 days/week, for 3 weeks. All animals were sacrificed at the end of 18 months. Routine gross and microscopic evaluation of the stomach and intestines at 18 months revealed no persistent adverse effects.

Hematological Effects. Leukocytosis persisting for approximately 12 hours after fever dissipates is one of the hallmarks of metal fume fever (Mueller and Seger 1985). Such effects have been observed in a number of case reports of occupational and experimental exposure of humans to zinc oxide fumes (Brown 1988; Drinker et al. 1927a; Malo et al. 1990; Rohrs 1957; Sturgis et al. 1927). Increased leukocyte counts were observed following experimental exposures to 430 mg zinc/m^3 as zinc oxide for 3 hours (Drinker et al. 1927a) or 600 mg zinc/m^3 as zinc oxide for lo-12 minutes (Sturgis et al. 1927). These studies are limited in that they used an inadequate number of subjects, lacked controls, and used impure zinc oxide.

Decreased numbers of red blood cells and hemoglobin were found in several workers with 7-20 years of experience in the galvanizing industry (McCord et al. 1926). However, there were excess tobacco use and alcohol consumption by workers and possible concurrent exposure to other chemicals (chloride, sulfide) which limit the study results. No anemia was detected among 12 workers exposed for 4-21 years to zinc oxide fumes in the production of brass alloys (Hamdi 1969). These workers may have also been exposed to magnesium, copper, and aluminum.

No studies were located regarding hematological effects in animals after inhalation exposure to zinc.

Hepatic Effects. Routine blood chemistries and examinations revealed no liver disease among 12 workers with 4-21 years of exposure to zinc oxide fumes in the production of brass alloys (Hamdi 1969).

No adverse effects were observed during gross and microscopic examination of livers of rats and guinea pigs exposed to 121.7 mg zinc/m^3 or 119.3 mg zinc/m^3, respectively, as zinc chloride smoke for 1 hour/day, 5 days/week, for 20 weeks, and then sacrificed at the end of 18 months (Marrs et al. 1988). Significant increases in the incidence of fatty liver were observed in mice exposed to 12.8 or 121.7 mg zinc/m^3 as zinc chloride smoke using the same exposure paradigm; however, the incidence did not increase with dose (Marrs et al. 1988). The smoke contained other compounds in addition to zinc chloride.

Renal Effects. Urinalyses and histories of urinary function revealed no adverse effects in 24 workers exposed for 2-35.5 years to 5130 mg zinc/m^3 as metallic zinc dust, zinc sulfide dust, zinc oxide, or lithophone dust (Batchelor et al. 1926).

No adverse effects were observed following gross and microscopic examination of kidneys from rats, mice, and guinea pigs exposed for 1 hour/day, 5 days/week, for 20 weeks, to concentrations as high as 121.7 or 119.3 mg zinc/m^3 as zinc chloride smoke (which also contained other compounds) and then sacrificed 13 months later (Marrs et al. 1988).

Dermal/Ocular Effects. Reddened conjunctiva and cornea1 burns occurred in individuals exposed to high concentrations of zinc chloride smoke (estimated at 33,000 mg zinc/m^3) when several smoke generators exploded in a tunnel during World War II (Evans 1945). The ocular effects may have been due to direct contact with the smoke.

Other Systemic Effects. A fever appearing 3-10 hours after exposure to zinc oxide fumes and lasting approximately 24-48 hours is characteristic of metal fume fever caused by zinc (Mueller and Seger 1985). Elevated body temperature has been observed in a number of experimental and occupational zinc oxide exposures (Brown 1988; Drinker et al. 1927a; Hammond 1944; Malo et al.

1990; Rohrs 1957; Sturgis et al. 1927; Vogelmeier et al. 1987). Using a number of exposure concentrations for various durations, Drinker et al. (1927b) found that the increase in body temperature was dependent on the exposure duration and concentration. Based on their data, they calculated that the threshold for pyrogenic effects was 45 mg zinc/m^3 for 20 minutes. This study is limited in that impurities were present in the zinc used and no statistical analysis was performed. Exposure to zinc chloride smoke (which also contains other compounds) has also been associated with fever (Hjortso et al. 1988; Matarese and Matthews 1966).

No studies were located regarding other systemic effects in animals following inhalation exposure to zinc.

2.2.1.3 Immunological Effects

One report described hives and angioedema in a man exposed to zinc fumes at a zinc smelting plant (Farrell 1987). The author suggested that the patient had an immediate or delayed immunoglobulin E (IgE) response (or both) after a low dose of zinc fumes. Metal fume fever also resulted when the exposure increased. The signs and symptoms of toxicity were repeated in a challenge test conducted at the patient's home.

In a group of 14 welders acutely exposed to 77-153 mg zinc/m^3 as zinc oxide, significant correlations between the concentration of airborne zinc and the proportion of activated T cells, T helper cells, T inducer cells, T suppressor cells, and activated killer T cells were observed 20 hours after exposure (Blanc et al. 1991). In addition, significant increases in levels of polymorphonuclear leukocytes, macrophages, and all types of lymphocytes were observed in the bronchoalveolar lavage fluid 20 hours after exposure. Increased levels of lymphocytes, with a predominance of CD8 cells, in the bronchoalveolar lavage fluid were reported in a case study of a smelter exposed to unspecified levels of zinc fumes (Ameille et al. 1992).

The bronchoalveolar lavage fluid of rats or guinea pigs exposed to 2.2 mg zinc/m^3 for 3 hours contained increased levels of β-glucuronidase, suggesting a change in macrophage function (Gordon et al. 1992). Rabbits were not affected following a similar exposure to 4.6 mg zinc/m^3 for 2 hours. Rats, mice, and guinea pigs were exposed to concentrations as high as 119.3 or 121.7 mg zinc/m^3 as zinc chloride smoke for 1 hour/day, 5 days/week, for 20 weeks (Marrs et al.

1988). Routine gross and histopathologic examination of the lymph nodes, thymus, and spleen at the end of 18 months revealed no adverse effects. The smoke also contained zinc oxide, hexachlorophene, and other compounds.

2.2.1.4 Neurological Effects

Humans have reported nonspecific neurological effects such as headaches and malaise in association with other symptoms following inhalation of zinc oxide and in metal fume fever (Rohrs 1957; Sturgis et al. 1927). Staggering gait, hallucinations, and hilarity were observed in an individual who intentionally inhaled aerosols of metallic paint containing copper and zinc (Wilde 1975). However, it is most likely that these effects were due to exposure to hydrocarbon propellant rather than zinc.

No studies were located regarding neurological effects in animals after inhalation exposure to zinc.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to zinc.

Following an initial exposure of rats, mice, and guinea pigs to concentrations as high as 119.3 or 121.7 mg zinc/m^3 as zinc chloride smoke (which also contained other compounds) for 1 hour/day, 5 days/week, for 20 weeks, no adverse effects on the mammary glands, ovaries, fallopian tubes, or uteri were observed at 18 months (Marrs et al. 1988).

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to zinc.

2.2.1.7 Genotoxic Effects

Chromosome aberrations were observed in the lymphocytes of 24 workers in a zinc smelting plant (Bauchinger et al. 1976). However, the workers had increased blood levels of lead and cadmium, and the clastogenic effect was attributed to cadmium exposure.

Mice exposed by inhalation to zinc oxide had an increase in chromosomal aberrations in bone marrow cells (Voroshilin et al. 1978).

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

In two epidemiological studies, workers did not have an increased incidence of cancers associated with occupational exposure (primarily inhalation exposure) to zinc (Logue et al. 1982; Neuberger and Hollowell 1982).

Workers in nine electrolytic zinc and copper refining plants were studied by Logue et al. (1982). The workers at two of these plants were exposed to zinc or zinc and copper; the other workers were exposed to copper. An association between cancer mortality and zinc exposure was not found.

Excess lung cancer mortality associated with residence in an old lead/zinc mining and smelting area of the midwestern United States was studied by Neuberger and Hollowell (1982). The ageand sex-adjusted mortality rates were compared to state and national rates. The analysis determined that lung cancer mortality was elevated in the region but was not found to be associated with exposure to environmental levels of lead or zinc. Many confounding factors were not considered in the analysis, such as smoking, occupation, and duration of residence in the area in question.

Female Porton strain mice (98-l00/group) exposed to 121.7 mg zinc/m^3 of a zinc oxide/ hexachloroethane smoke mixture (which produces zinc chloride), 1 hour/day, 5 days/week, for 20 weeks had a statistically significant increase in the incidence of alveologenic carcinoma (30%

versus 8% in control) thirteen months after the end of exposure (Marrs et al. 1988). No increased tumor incidences were seen in mice exposed to 1, 1.3, or 12.8 mg zinc/m^3. Guinea pigs and rats were also tested with similar dose levels, and no significant carcinogenic response was observed. A number of factors limits the usefulness of this study, including the presence of several compounds in the smoke that may have carcinogenic potential, the use of only female animals, and the short duration of the exposure (20 weeks).

2.2.2 Oral Exposure

Zinc has been orally administered in a variety of forms, such as zinc chloride, zinc sulfate, zinc oxide, powdered zinc, and others. Some of these compounds, such as zinc sulfate, have been administered in both hydrated and anhydrous forms. Study authors often do not state definitely which form was used in a particular study. Knowledge of the form used and its molecular weight is necessary to calculate the amount of elemental zinc administered under a given set of circumstances. If adequate information was not reported by the study authors, it was assumed that an anhydrous compound was used.

2.2.2.1 Death

In a case report presented by Murray (1926), an infant died from bronchopneumonia resulting from inhalation and ingestion of an unspecified amount of zinc stearate powder spilled from a container. However, the cause of death (bronchopneumonia) suggests that it resulted from the inhalation exposure, rather than the oral exposure, and it is unclear whether the lung damage resulted from the inhalation of zinc stearate powder specifically or from the inhalation of powders in general.

The LD_{50} values of several zinc compounds have been determined in rats and mice (Domingo et al. 1988a). In general, mice appear to be more sensitive than rats to the lethal effects of zinc. In rats, zinc acetate was the most lethal compound tested; zinc nitrate, zinc chloride, and zinc sulfate (in order of decreasing toxicity) were less lethal. In mice, the most lethal compound was zinc acetate followed by zinc nitrate, zinc sulfate, and zinc chloride. Ingestion of 390 mg zinc/kg/day as zinc oxide in the diet for 3-13 days was lethal to ferrets (Straube et al. 1980). An equivalent dose in humans would be approximately 27 g zinc/day (which would probably be intolerable to humans

because of gastric discomfort). Death was reported in mice that consumed 1,110 mg zinc/kg/day as zinc sulfate in their diet for 13 weeks (Maita et al. 1981). Mortality was also observed in 20% of rats ingesting 191 mg zinc/kg/day as zinc acetate in drinking water for 3 months (Llobet et al. 1988a).

The LD_{50} values and all LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

Ingestion of zinc or zinc-containing compounds has resulted in a variety of systemic effects in the gastrointestinal and hematological systems and alterations in the blood lipid profile in humans and animals. In addition, lesions have been observed in the liver, pancreas, and kidneys of animals. No studies were located regarding respiratory effects in humans or animals after oral exposure to zinc.

Observed systemic effects after oral exposure are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. The effects discussed in case reports are not included in Table 2-2 or Figure 2-2 because of the small sample size and lack of control data.

Cardiovascular Effects. A number of studies in humans and animals have examined the effects of zinc on serum cholesterol and triglycerides. These data are discussed below under Other Systemic Effects. However, no studies regarding the direct relationship between excessive zinc intake and cardiac mortality were located. No effects on electrocardiographic results were found in a group of elderly subjects (>65 years of age) taking zinc supplements of up to 2 mg zinc/kg/day (Hale et al. 1988) or 0.71 mg zinc/kg/day (Czerwinski et al. 1974). There was also no effect on the frequency of cardiovascular disease (heart attack, heart failure, hypertension, or angina) in elderly subjects (>67 years of age) taking up to 2 mg zinc/kg/day (Hale et al. 198s).

In one study, patients having inoperable severe occlusive vascular disease were administered 3.8 mg zinc/kg/day as zinc sulfate for at least 1 year (Henzel et al. 1971). Eighteen of the

TABLE 2-2. Levels of Significant Exposure to Zinc - Oral

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Zn/kg/day)	LOAEL (effect) Less serious (mg Zn/kg/day)	LOAEL (effect) Serious (mg Zn/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Rat	(G)	Once				237 (LD50)	Domingo et al. 1988a	acetate
2	Rat	(G)	Once				623 (LD50)	Domingo et al. 1988a	sulfate
3	Rat	(G)	Once				528 (LD50)	Domingo et al. 1988a	chloride
4	Rat	(G)	Once				293 (LD50)	Domingo et al. 1988a	nitrate
5	Mouse	(G)	Once				337 (LD50)	Domingo et al. 1988a	sulfate
6	Mouse	(G)	Once				86 (LD50)	Domingo et al. 1988a	acetate
7	Mouse	(G)	Once				605 (LD50)	Domingo et al. 1988a	chloride
8	Mouse	(G)	Once				204 (LD50)	Domingo et al. 1988a	nitrate
9	Ferret	(F)	<2 wk				390 (3/3 died)	Straube et al. 1980	oxide
Systemic									
10	Human	(W)	Once	Other Other (serum glucose and insulin)	0.5	0.5 (decreased serum cortisol levels)		Brandao-Neto et al. 1990a	sulfate
11	Human	(W)	Once	Gastro		6.7 (gastrointestinal distress; diarrhea)		Callender and Gentzkow 1937	oxide

TABLE 2-2. Levels of Significant Exposure to Zinc - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Zn/kg/day)	LOAEL (effect) Less serious (mg Zn/kg/day)	LOAEL (effect) Serious (mg Zn/kg/day)	Reference	Form
12	Human	(F)	2 d	Gastro Other	86	86 (increased serum amylase, lipase)		Murphy 1970	elemental
Neurological									
13	Rat	(G)	10 d 1x/d			487 (minor neuronal degeneration; decreased acid phosphatase and acetylcholinesterase; increased thiamine pyrophosphatase)		Kozik et al. 1980	oxide
INTERMEDIATE EXPOSURE									
Death									
14	Rat	(W)	3 mo ad lib				191 (2/10 died)	Llobet et al. 1988a	acetate
15	Mouse	(F)	13 wk ad lib				1110 (5/24 died)	Maita et al. 1981	sulfate
Systemic									
16	Human	(C)	12 wk 1x/d	Other		0.71 (decreased serum HDL-cholesterol)		Black et al. 1988	gluconate
17	Human	(C)	5 wk 2x/d	Other		2.3 (decreased serum HDL-cholesterol)		Hooper et al. 1980	sulfate
18	Human	(C)	10 wk 7d/wk 2x/d	Hemato		0.83[b] (decreased superoxide dismutase activity, hematocrit, and serum ferritin)		Yadrick et al. 1989	gluconate

TABLE 2-2. Levels of Significant Exposure to Zinc - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Zn/kg/day)	LOAEL (effect) Less serious (mg Zn/kg/day)	LOAEL (effect) Serious (mg Zn/kg/day)	Reference	Form
19	Human	(F)	6 wk 3x/d	Gastro		2.0 (abdominal cramps; vomiting; nausea)		Samman and Roberts 1987	sulfate
20	Human	(C)	6 wk 7d/wk 3x/d	Other (HDL-cholesterol, LDL-cholesterol)	2.4			Samman and Roberts 1988	sulfate
21	Human	(C)	6 wk 7d/wk 2x/d	Hemato		0.71 (decreased superoxide dismutase activity)		Fischer et al. 1984	gluconate
22	Human	(C)	24 wk 7d/wk 3x/d	Cardio	0.71			Czerwinski et al. 1974	sulfate
23	Human	(C)	3 mo 7d/wk 1x/d	Other (HDL-cholesterol)	1.5			Bogden et al. 1988	acetate
24	Human	(C)	6 wk 2x/d	Other		4.3 (increased serum LDL-cholesterol; decreased serum HDL-cholesterol)		Chandra 1984	sulfate
25	Rat	(F)	13 wk ad lib	Gastro	565			Maita et al. 1981	sulfate
				Hemato	53	565 (decreased hematocrit and WBC)			
				Musc/skel	565				
				Renal	565				
				Other	53		565 (acinar cell necrosis and metaplasia in pancreas)		
26	Rat	(F)	6 wk 7d/wk ad lib	Hemato		6 (ceruloplasmin reduced by 28%)		L'Abbe and Fischer 1984a	sulfate

TABLE 2-2. Levels of Significant Exposure to Zinc - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Zn/kg/day)	LOAEL (effect) Less serious (mg Zn/kg/day)	LOAEL (effect) Serious (mg Zn/kg/day)	Reference	Form
27	Rat	(W)	4 wk 7d/wk ad lib	Hemato		12 (decreased Hb and erythrocytes)		Zaporowska and Wasilewski 1992	chloride
28	Rat	(F)	5 wk ad lib	Hemato		500 (decreased Hb, hematocrit, MCH, MCHC; slightly increased WBC)		Smith and Larson 1946	carbonate
29	Rat	(W)	3 mo ad lib	Hemato	191			Llobet et al. 1988a	acetate
				Hepatic	191				
				Renal	95		191 (increased plasma creatinine and urea levels; desquamation of epithelial cells of proximal tubules)		
				Other (body weight)	191				
30	Rat	(F)	6 wk ad lib	Hemato		350 (decreased Hb)		Smith and Larson 1946	carbonate
31	Rabbit	(F)	22 wk daily	Hemato		174 (slight decrease in Hb levels)		Bentley and Grubb 1991	carbonate
				Other (body weight)	174				
32	Mouse	(F)	13 wk ad lib	Gastro	104		1110 (ulceration of forestomach)	Maita et al. 1981	sulfate
				Hemato	104	1110 (decreased WBC; anemia)			
				Renal	104	1110 (unspecified regressive lesions)			
				Other	104		1110 (acinar cell necrosis and metaplasia in pancreas)		
33	Mouse	(F)	9 mo ad lib	Hemato			68 (severe anemia)	Walters and Roe 1965	oleate

TABLE 2-2. Levels of Significant Exposure to Zinc - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Zn/kg/day)	LOAEL (effect) Less serious (mg Zn/kg/day)	LOAEL (effect) Serious (mg Zn/kg/day)	Reference	Form
34	Dog	(W)	9 mo ad lib	Musc/skel	4			Anderson and Danylchuk 1979	oxide
35	Ferret	(F)	7-97 d ad lib	Gastro	195		390 (intestinal hemorrhages)	Straube et al. 1980	oxide
				Hemato	65	195 (anemia)			
				Renal	65	195 (nephrosis)			
				Other	195	390 (pancreatitis)			
36	Mink	(F)	144 d ppd70-214	Hemato	323.6			Aulerich et al. 1991	sulfate
				Hepatic	323.6				
				Renal	323.6				
				Other (body weight)	323.6				
37	Cow	(F)	5 wk 2x/d ppd3-40	Hemato		64 (decreased hematocrit levels)		Jenkins and Hidiroglou 1991	oxide
				Other	64		91 (body weight gain decreased 46%)		
Immunological									
38	Human	(C)	6 wk 2x/d			4.3 (impaired lymphocyte and polymorphonuclear leukocyte function)		Chandra 1984	sulfate
39	Human	(C)	3 mo 7d/wk 1x/d		1.5			Bogden et al. 1988	acetate
40	Human	(C)	1 mo 2x/d		2.5			Duchateau et al. 1981	sulfate
41	Mouse	(F)	4 wk 7d/wk ad lib		76.9			Schiffer et al. 1991	sulfate
42	Mouse	(F)	8 wk 7d/wk ad lib		6.5			Fernandes et al. 1979	NS

TABLE 2-2. Levels of Significant Exposure to Zinc - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Zn/kg/day)	LOAEL (effect) Less serious (mg Zn/kg/day)	LOAEL (effect) Serious (mg Zn/kg/day)	Reference	Form
Developmental									
43	Human	(C)	Gwk 20 through parturition		0.3			Mahomed et al. 1989	sulfate
44	Human	(C)	last 15-25 wk of pregnancy 1x/d		0.3			Simmer et al. 1991	citrate
45	Human	(C)	11 wk 1x/d		0.06			Kynast and Saling 1986	aspartate
46	Rat	(F)	20 d Gd0-20 ad lib		25			Uriu-Hare et al. 1989	carbonate
47	Rat	(F)	15 d Gd1-15 ad lib				200 (29% fetal resorption; decreased fetal weight)	Schlicker and Cox 1968	oxide
48	Rat	(F)	36 d Gd1-15 ad lib		100			Schlicker and Cox 1968	oxide
49	Rat	(F)	150 d ad lib		50		250 (increased stillbirths)	Sutton and Nelson 1937	carbonate
50	Rat	(F)	7 wk Gd0-17 ad lib		250			Kinnamon 1963	carbonate
51	Rat	(F)	36 d Gd1-21 ad lib				200 (100% fetal resorption)	Schlicker and Cox 1968	oxide
52	Mouse	(F)	2 gen			260 (alopecia; decreased hematocrit)		Mulhern et al. 1986	carbonate

TABLE 2-2. Levels of Significant Exposure to Zinc - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Zn/kg/day)	LOAEL (effect) Less serious (mg Zn/kg/day)	LOAEL (effect) Serious (mg Zn/kg/day)	Reference	Form
53	Mink	(F)	approx 25 wk ad lib		20.8			Bleavins et al. 1983	sulfate
Reproductive									
54	Human	(C)	Gwk 20 through parturi-tion		0.3			Mahomed et al. 1989	sulfate
55	Rat	(F)	150 d ad lib		50		250 (no reproduction in females)	Sutton and Nelson 1937	carbonate
56	Rat	(F)	8 wk 7d/wk ad lib			25 (altered sperm chromatin structure)		Evenson et al. 1993	chloride
57	Rat	(F)	18 d Gd0-18 ad lib				200 (increased pre-implantation loss)	Pal and Pal 1987	sulfate
58	Mouse	(F)	13 wk ad lib		1110			Maita et al. 1981	sulfate
59	Mink	(F)	approx 25 wk ad lib		20.8			Bleavins et al. 1983	sulfate
CHRONIC EXPOSURE									
Systemic									
60	Human	(C)	8 yr 7d/wk 1x/d	Cardio Hemato Other (cholesterol)	2.0 2.0	 2.0 (decreased RBC) 		Hale et al. 1988	NS

TABLE 2-2. Levels of Significant Exposure to Zinc - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Zn/kg/day)	LOAEL (effect) Less serious (mg Zn/kg/day)	LOAEL (effect) Serious (mg Zn/kg/day)	Reference	Form
61	Mouse	(W)	5-14 mo ad lib	Other		70 (hypertrophy and vacuolation of pancreas islet cells; hypertrophy and vacuolization of fasciculata cells in adrenal cortex)		Aughey et al. 1977	sulfate

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive intermediate oral minimal risk level (MRL) of 0.3 mg/kg/day. The sum of the reported supplemental dose (0.83 mg/kg/day) and the estimate from the FDA Total Diet Study for 1982-1986 (0.16 mg/kg/day) resulted in a total dose of 1 mg/kg/day. The total dose was then divided by an uncertainty factor of 3 (based on minimal LOAEL from a study of the most sensitive humans and the consideration that zinc is an essential dietary nutrient). The intermediate oral MRL was adopted as the chronic oral MRL.

acetate = zinc acetate; ad lib = ad libitum; approx = approximately; aspartate = zinc aspartate; (C) = capsule; carbonate = zinc carbonate; Cardio = cardiovascular; chloride = zinc chloride; citrate = zinc citrate; d = day(s); elemental = elemental zinc; (F) = feed; (G) = gavage, not specified; Gastro = gastrointestinal; Gd = gestation day; gen = generation; gluconate = zinc gluconate; Gwk = gestation week; Hb = hemoglobin; HDL = high density lipoprotein; Hemato = hematological; LD50 = lethal dose, 50% kill; LDL = low density lipoprotein; LOAEL = lowest-observed-adverse-effect level; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; mo = month(s); Musc/skel = musculoskeletal; nitrate = zinc nitrate; NOAEL = no-observed-adverse-effect level; NS = not specified; oleate = zinc oleate; oxide = zinc oxide; ppd = post partum day; RBC = red blood cell; sulfate = zinc sulfate; (W) = drinking water; WBC = white blood cell; wk = week(s); x = time(s); yr = year(s); Zn = zinc

FIGURE 2-2. Levels of Significant Exposure to Zinc - Oral

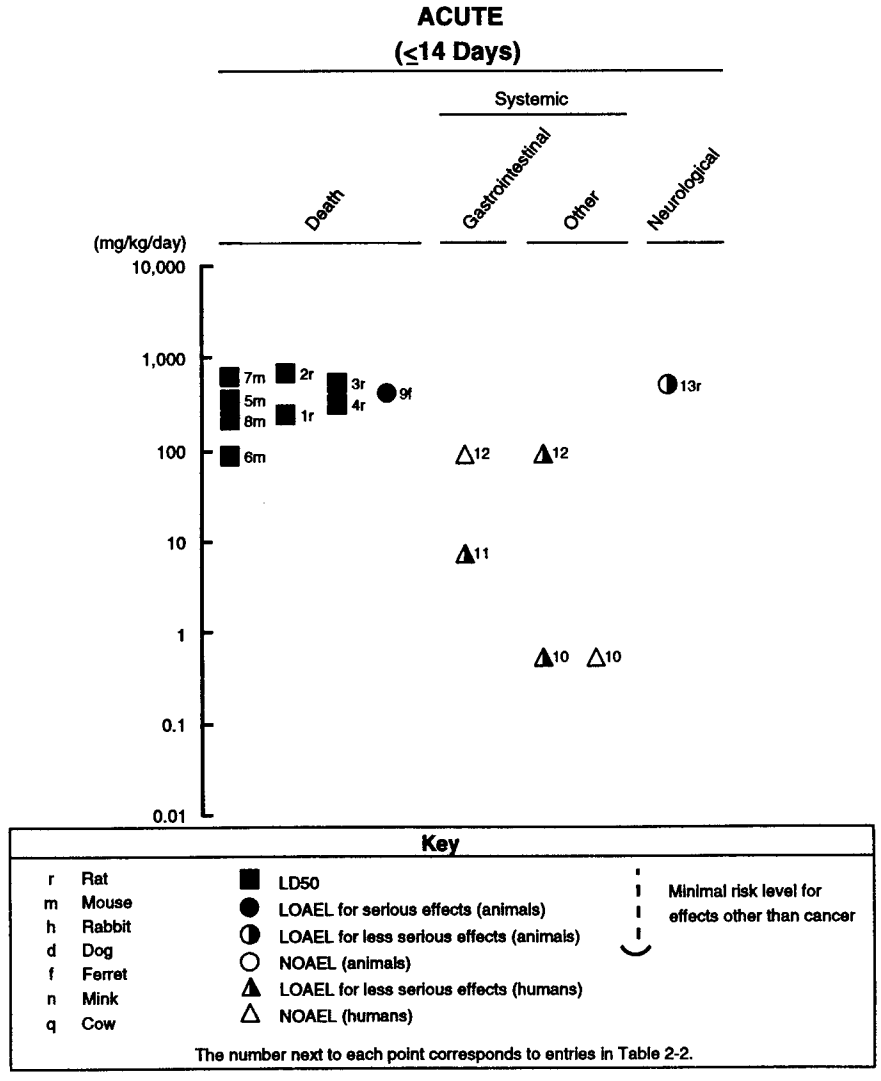


FIGURE 2-2. Levels of Significant Exposure to Zinc - Oral *(continued)*

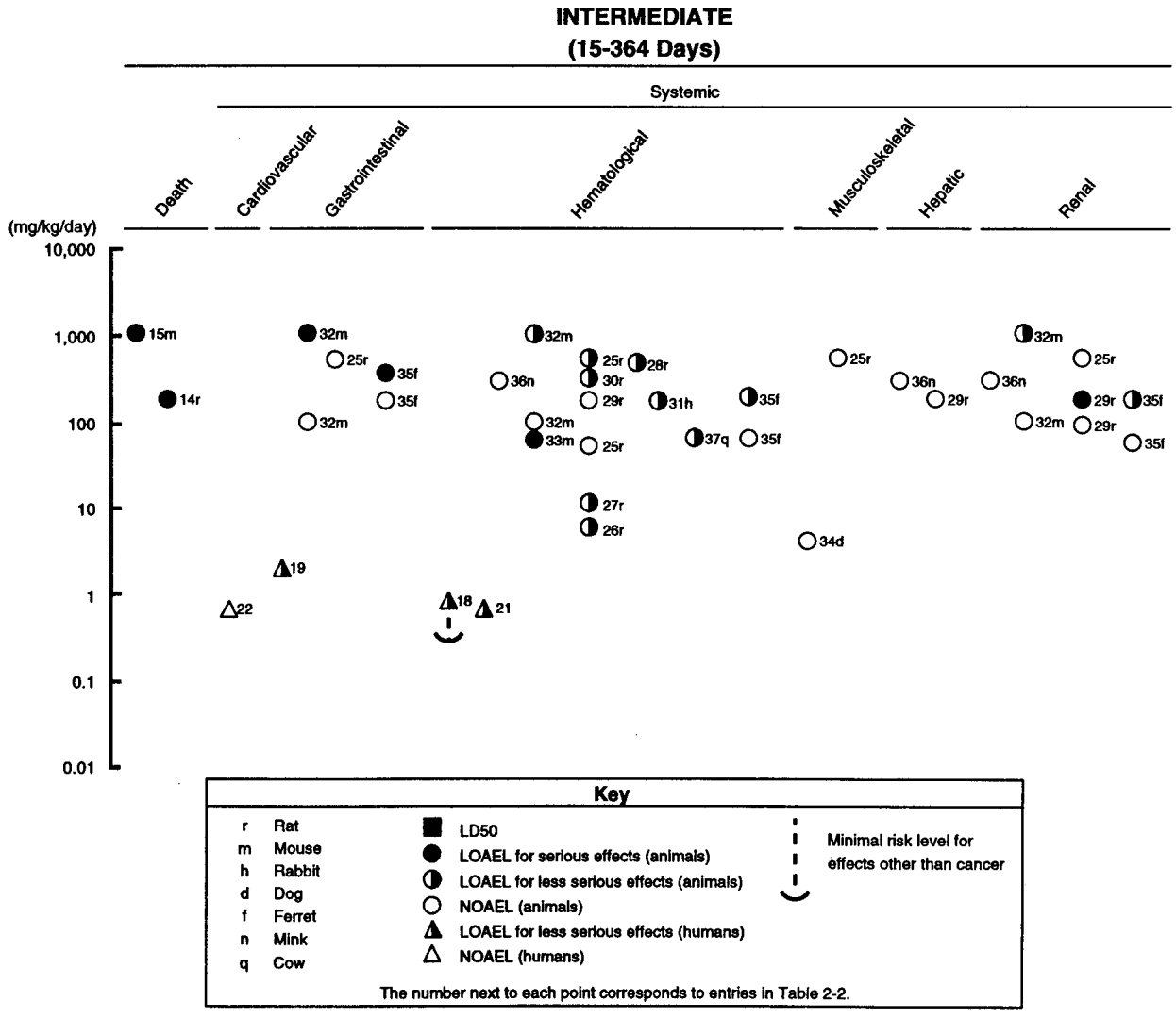


FIGURE 2-2. Levels of Significant Exposure to Zinc - Oral *(continued)*

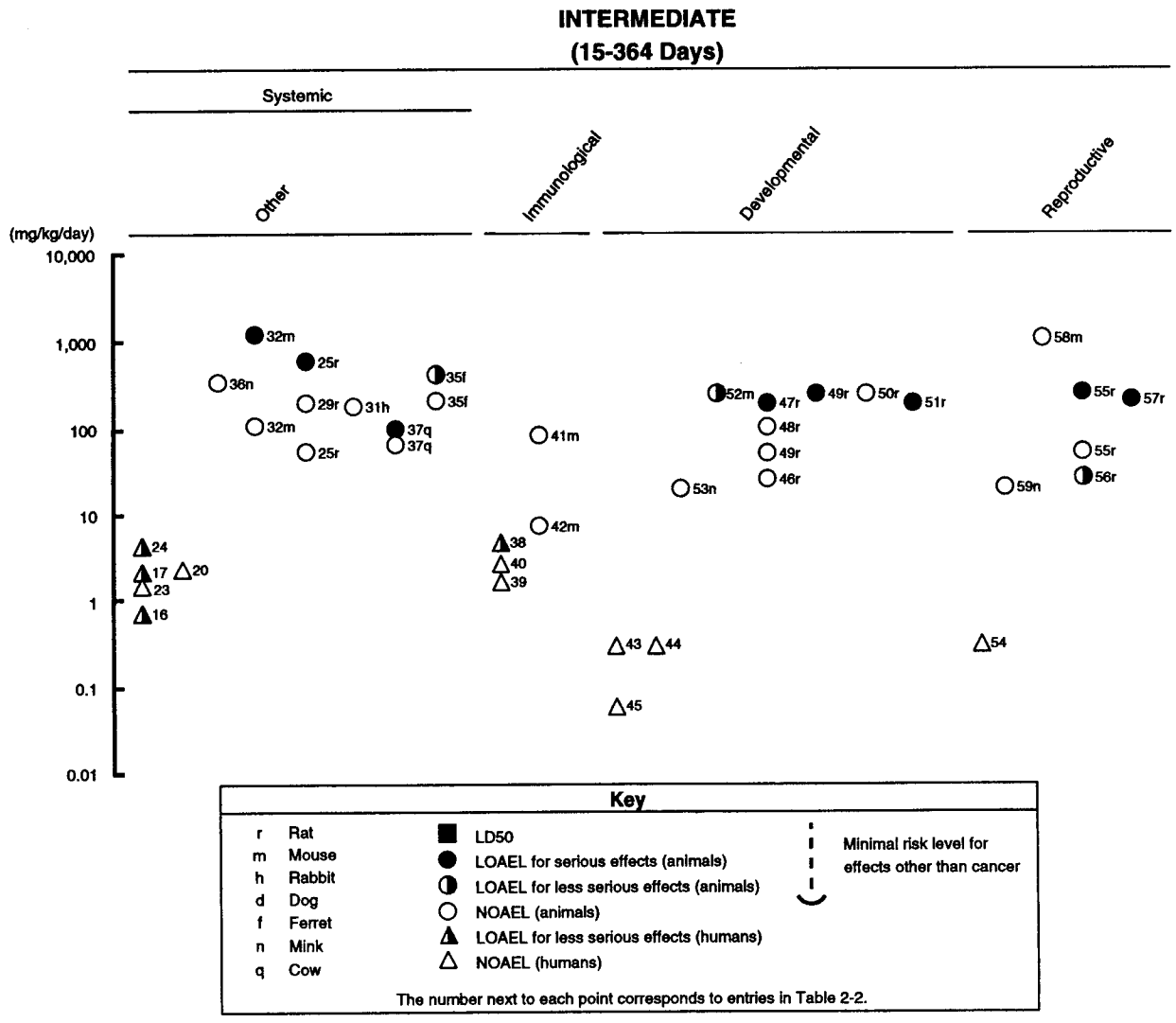
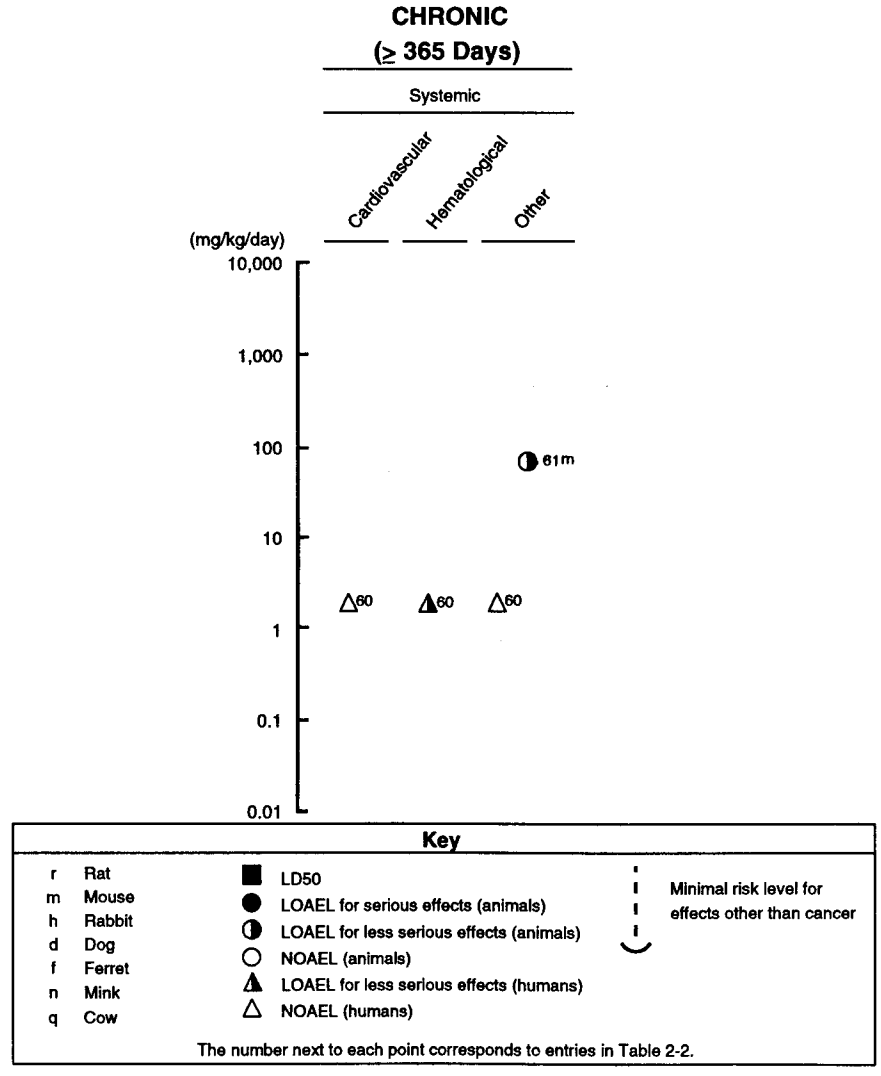


FIGURE 2-2. Levels of Significant Exposure to Zinc - Oral *(continued)*



24 patients experienced improvement in lower extremity blood flow and unchanged or decreased arterial pressure. Zinc's role in these improvements was not completely understood by the study authors. They hypothesized that when optimal zinc levels are provided to the ischemic limb, the activity of certain zinc enzymes promotes the reversal of tissue-dependent hypoxia and/or lactic acidemia in the muscles. It is also not known if this high dose of zinc was associated with any toxic effects.

No studies were located regarding cardiovascular effects in animals after oral exposure to zinc.

Gastrointestinal Effects. Several studies have suggested that zinc ingestion may cause symptoms of gastrointestinal distress or alterations in gastrointestinal tissues. For example, one individual who ingested about 3 ounces of a zinc chloride solution described acute symptoms that occurred almost immediately following contact with the compound, including burning and pain in the mouth and throat and vomiting (Chobanian 1981). Later, the patient exhibited pharyngitis, esophagitis, hypocalcemia, and elevated levels of amylase; the latter two alterations are suggestive of acute pancreatitis. The patient received intravenous hydration and calcium supplementation and recovered within 5 days. The material ingested was described as a "zinc chloride solution," and its concentration was not reported. Therefore, a dose level could not be established in this case.

Several cases of gastrointestinal disturbances have been reported after ingestion of large amounts of zinc as zinc sulfate (Anonymous 1983; Brown et al. 1964; Moore 1978; Samman and Roberts 1987). Vomiting, abdominal cramps, and diarrhea, in several cases with blood, have been observed after ingestion of zinc sulfate. In one report, an English school girl ingested 440 mg zinc sulfate/day (2.6 mg zinc/kg/day) in capsules as a medically prescribed treatment for acne (Moore 1978). After taking each capsule, she experienced epigastric discomfort. A week later, she was admitted to the hospital after a fainting spell. She was diagnosed as anemic and subsequently passed melanic stools, indicative of gastrointestinal bleeding. Gastrointestinal upset (abdominal cramps, vomiting, nausea) occurred in 26 of 47 healthy volunteers following ingestion of zinc sulfate tablets (150 mg as zinc ion in three divided doses per day, 2 mg zinc/kg/day) for 6 weeks (Samman and Roberts 1987). Ingestion of zinc oxide has also been associated with gastrointestinal distress (Anonymous 1983; Callender and Gentzkow 1937). In one case, 80% of the personnel of two army companies became ill with gastrointestinal distress and diarrhea after

consuming limeade prepared in galvanized trash cans (Callender and Gentzkow 1937). The average dose was estimated to be 6.7-7.1 mg/kg. A second example was presented in a case involving school children in New Mexico who experienced nausea and vomiting after accidental excessive zinc intake (Anonymous 1983). These children had consumed punch containing high levels of zinc dissolved from galvanized hinges attached to tanks in which the punch was stored. A 16-year-old boy who ingested 12 g elemental zinc over a 2-day period (86 mg zinc/kg/day) experienced light-headedness, lethargy, staggering gait, and difficulty writing legibly, but no apparent gastrointestinal disturbances (Murphy 1970).

Gastrointestinal effects have also been observed in animals. Intestinal hemorrhages were observed in ferrets that ingested 390 mg zinc/kg/day as zinc oxide for 2 weeks (Straube et al. 1980). These ferrets exhibited a 75% reduction in food intake. No intestinal hemorrhaging was observed in ferrets fed 195 mg/kg/day for up to 21 days. Oral zinc sulfate exposures of intermediate duration in other experimental animals have also resulted in gastrointestinal effects. Mice fed a diet providing 1,110 mg zinc/kg/day developed ulcers in the forestomach, but gastrointestinal effects were not observed in rats fed 565 mg zinc/kg/day (Maita et al. 1981).

Hematological Effects. In a case report, acute exposure to 2.6 mg zinc/kg/day as zinc sulfate for 1 week resulted in anemia (Moore 1978). The authors of the report noted that the anemia may have been secondary to the gastrointestinal hemorrhages.

Treatment-related changes in hematological parameters have been observed in humans and animals after intermediate or chronic exposure to zinc or zinc-containing compounds. Long-term administration (l-8 years) of zinc supplements has caused anemia in humans (Broun et al. 1990; Gyorffy and Chan 1992; Hale et al. 1988; Hoffman et al. 1988; Patterson et al. 1985; Porter et al. 1977; Prasad et al. 1978; Ramdurai et al. 1993; Stroud 1991; Summerfield et al. 1992). Exposure to 2 mg zinc/kg/day as zinc sulfate for 10 months resulted in anemia (Hoffman et al. 1988). A significant reduction in erythrocyte superoxide dismutase activity (47% decrease), hematocrit, and serum ferritin, compared to pretreatment levels, occurred in female subjects who received supplements (as capsules) of 50 mg zinc/day as zinc gluconate for 10 weeks (Yadrick et al. 1989). A 15% decrease in erythrocyte superoxide dismutase activity was reported in male volunteers receiving 50 mg zinc/day as zinc gluconate for 6 weeks (Fisher et al. 1984).

In animals, following oral administration of zinc compounds, decreased hemoglobin, hematocrit, erythrocyte, and/or leukocyte levels were observed in rats (Maita et al. 1981; Smith and Larson 1946), mice (Maita et al. 1981; Walters and Roe 1965) rabbits (Bentley and Grubb 1991) dogs (Drinker et al. 1927d; Meurs et al. 1991; Robinson et al. 1991), ferrets (Straube et al. 1980), and preruminant calves (Jenkins and Hidiroglou 1991). In rats, the lowest LOAEL for decreased hemoglobin (85% of control value) is 12 mg zinc/kg/day as zinc chloride in a 4-week drinking water study with 2-month-old rats (Zaporowska and Wasilewski 1992). The highest NOAEL in rats is 191 mg zinc/kg/day as zinc acetate in a 3-month drinking water study (age of rats not specified) (Llobet et al. 1988a). The reason that the lowest LOAEL is less than the highest NOAEL in rats is unclear, but it may be because of the use of different zinc compounds or different rat strains or age. The second lowest rat LOAEL is 350 mg zinc/kg/day as zinc carbonate (Smith and Larson 1946). For mice, NOAEL and LOAEL values of 104 and 1,110 mg zinc/kg/day as zinc sulfate, respectively, were identified by Maita et al. (1981) in a 13-week feeding study. A LOAEL of 68 mg zinc/kg/day as zinc oleate was observed in a 9-month mouse feeding study (Walters and Roe 1965). It is not known if the difference in the LOAELs identified in the Maita et al. (1981) and Walters and Roe (1965) studies is due to the use of different zinc compounds, different basic diet formulations, different mouse strains, or different exposure durations. Slight decreases in hemoglobin levels were observed in rabbits fed 174 mg zinc/kg/day as zinc carbonate (Bentley and Grubb 1991). Zinc oxide consumption caused anemia in dogs (76.5 mg zinc/kg/day) (Drinker et al. 1927d), ferrets (195 mg zinc/kg/day) (Straube et al. 1980) and preruminant calves (64 mg zinc/kg/day) (Jenkins and Hidiroglou 1991). Hematological alterations were not observed in cats exposed to up to 83.2 mg zinc/kg/day as zinc oxide (Drinker et al. 1927d) or in adult mink exposed to zinc at up to 297.4 mg zinc/kg/day as zinc oxide (Aulerich et al. 1991; Bleavins et al. 1983). However, decreases in hematocrit and lymphocytes were observed in the offspring of mink females that ingested a time-weighted-average dose of 20.8 mg zinc/kg/day as zinc sulfate for 10 weeks prior to conception and throughout gestation and lactation (Bleavins et al. 1983) indicating that very young mink may be more sensitive to the hematologic effects of zinc than adults. An increased number of weanling rats had low levels of ceruloplasmin, a copper serum protein, after administration of zinc sulfate for 6 weeks (Abbe and Fischer 1984a).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to zinc.

Rib biopsies revealed no treatment-related effects in dogs given 4 mg zinc/kg/day as zinc oxide in the diet for 9 months (Anderson and Danylchuk 1979).

Hepatic Effects. Ingestion of 3.5 mg/kg/day zinc sulfate for 18 weeks by 13 patients being treated for chronic venous leg ulcers was reported to have no effect on the results of liver function tests (Hallbook and Lanner 1972). However, the type of liver function tests was not specified and results were not presented to support this conclusion.

No histopathology or changes in serum enzyme levels (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, or alkaline phosphatase) were observed in rats receiving 191 mg zinc/kg/day as zinc acetate (Llobet et al. 1988a). Similarly, no histopathology was observed in rats administered 98.3 mg zinc/kg/day as zinc oxide, but an insufficient number of animals were tested (Drinker et al. 1927c). Sheep fed time-weighted-average doses of 19 mg zinc/kg/day as zinc oxide for 49-72 days developed hepatic effects, including necrotic hepatocytes and large quantities of hemosiderin in Kupffer cells (Allen et al. 1983). Because sheep are ruminants, it is not known if they are a good model for predicting human toxicity. No histological damage was observed in adult or young mink fed 164.8 or 297.4 mg zinc/kg/day, respectively, as zinc sulfate for 144 days (Aulerich et al. 1991).

Decreased hexobarbital sleeping times were reported by Kadiiska et al. (1985) in rats receiving 40 mg zinc/kg/day as zinc sulfate. This physiological response suggested an induction of microsomal enzymes.

Renal Effects. Thirteen patients treated with zinc sulfate at 3.5 mg zinc/kg/day for 18 weeks for chronic venous leg ulcers had normal urinalyses (Hallbook and Lanner 1972). However, neither the specific parameters measured for the urinalysis nor the results were presented to support this conclusion. Furthermore, urinalysis may not be a sensitive indicator of renal function.

A number of intermediate-duration studies have demonstrated renal effects in animals exposed to zinc oxide, zinc sulfate, and zinc acetate. Zinc sulfate caused an increase in the absolute and relative kidney weights and regressive kidney lesions (not specified) in female mice that consumed 1,110 mg zinc/kg/day in the diet for 13 weeks, but no effects occurred in rats that consumed 565 mg zinc/kg/day under similar conditions (Maita et al. 1981). Severe diffuse

nephrosis was observed in ferrets exposed to 195 mg zinc/kg/day as zinc oxide in the diet (Straube et al. 1980). In rats exposed to 191 mg zinc/kg/day as zinc acetate for 3 months, epithelial cell damage in the glomerulus and proximal convoluted tubules and increased plasma creatinine and urea levels were observed (Llobet et al. 1988a). The NOAEL for the effects on creatinine and urea was 95 mg zinc/kg/day. It is unclear whether the microscopic changes were observed at lower doses. No histopathological changes in the kidneys were observed in three rats that drank water containing 98.3 mg zinc/kg/day as zinc oxide for 35-36 weeks (Drinker et al. 1927c); however, interpretation of the results of this study is severely limited by the small number of rats used. Renal tubular dilation, with proteinaceous casts and hemosiderin deposits, was observed in the kidneys of sheep that ingested 18 mg zinc/kg/day as zinc oxide for 49-72 days (Allen et al. 1983). It is not known if sheep are a good model for human toxicity because they are ruminants. No renal effects were observed in either adult mink consuming 326.7 mg zinc/kg/day as zinc sulfate or in young mink consuming 323.6 mg zinc/kg/day as zinc sulfate for 144 days (Aulerich et al. 1991).

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after oral exposure to zinc.

No dermal effects were seen in female minks given a time-weighted dose of 20.8 mg zinc/kg/day as zinc sulfate for 10 weeks prior to mating and then throughout gestation and lactation (Bleavins et al. 1983).

Other Systemic Effects

Pancreas. Increased levels of serum amylase were observed in a man after accidental ingestion of about 3 ounces of a zinc chloride solution (Chobanian 1981). A 16-year-old boy who ingested an average of approximately 86 mg zinc/kg/day as metallic zinc for 2 days (114 mg/kg on the 1st day and 57 mg/kg on the 2nd day) had increased serum amylase and lipase (Murphy 1970).

In humans receiving a single low dose of zinc sulfate (0.5 mg zinc/kg/day), no changes in blood glucose or insulin levels were observed, and there were no differences in response to a glucose load (Brandao-Neto et al. 1990b).

Pancreatic abnormalities (islet cellular alterations, acinar cell necrosis, metaplasia, fibrosis, pancreatitis) resulting from zinc ingestion have been observed in rats (Maita et al. 1981) mice (Aughey et al. 1977; Maita et al. 1981), cats (Drinker et al. 1927d), ferrets (Straube et al. 1980) sheep (Allen et al. 1983), and birds (Kazacos and Van Vleet 1989; Lu et al. 1990). In dogs (Drinker et al. 1927d) and minks (Aulerich et al. I991), histological changes in the pancreas have not been observed at doses comparable to or higher than the dose levels that caused abnormalities in rats, mice, cats, ferrets, and sheep. Degeneration of the acinar cells of the pancreas was observed in sheep by Allen et al. (1983) and in rats and mice by Maita et al. (1981). Since the pancreatic acinar cells secrete digestive juices into the small intestine, the increase in serum amylase and lipase observed in the human case reports (Chobanian 1981; Murphy 1970) would correspond to damage in this region of the pancreas.

In 2-month-old C3H mice exposed to 70 mg zinc/kg/day as zinc sulfate, hypertrophy and vacuolation of the β-cells of the pancreatic islets were observed beginning after 3 months of exposure and become more severe by 12 months (Aughey et al. 1977). The pancreatic islets secrete the hormones glucagon and insulin. No change in plasma levels of insulin and glucose was observed in this study after 6 months of exposure. No effect on islet cells was reported in rats exposed up to 565 mg/kg/day or mice exposed to 1110 mg/kg/day as zinc sulfate in a 13-week study by Maita et al. (1981) and Allen et al. (1983) reported that islet cells in sheep were generally unaffected, although occasional vacuolization occurred. Degeneration of acinar cells, but no effects on the islet cells, were found in ducklings (Kazacos and Van Vleet 1989); however, the relevance of this to humans is unclear. The data are too limited and contradictory to determine whether pancreatic islet cells are a primary target cell of zinc toxicity.

Adrenal Gland. Decreased levels of serum cortisol (a hormone secreted by the adrenal cortex) were observed in humans after a single dose of 0.5 mg zinc/kg/day as zinc sulfate (Brandao-Neto et al. 1990b). No effects on the adrenal gland itself have been reported in humans.
In mice receiving 70 mg zinc/kg/day as zinc sulfate in the drinking water, hypertrophy and increased lipid content of the zona fasciculata cells of the adrenal cortex were observed as early as 3 months after the start of zinc supplementation (Aughey et al. 1977).

Pituitary. No effects on pituitary function have been reported in humans following oral exposure to zinc. However, mice receiving 70 mg zinc/kg/day as zinc sulfate in the drinking water for 5-14 months had hypertrophy and increased granularity suggesting increased activity of the pituitary (Aughey et al. 1977). It is unclear whether the increased activity was a direct effect of the zinc or a reaction to decreased secretion from the adrenal cortex.

Serum Lipid Levels. Several reports described changes in the serum lipid profile of humans exposed to zinc sulfate or gluconate for 3-12 months; however, the results are mixed. Ingestion of 2.3-4.3 mg zinc/kg/day for 5-6 weeks (Chandra 1984; Hooper et al. 1980) or 0.71 mg zinc/kg/day for 12 weeks (Black et al. 1988) reduced levels of high-density lipoprotein (HDL) cholesterol. In the study by Chandra (1984) a slight increase in low-density lipoprotein (LDL) cholesterol was observed in subjects who served as their own controls; measurements were taken prior to zinc supplementation and after a lo-week postexposure period. Serum cholesterol, triglyceride, and LDL cholesterol levels were not affected by zinc supplementation in the study by Black et al. (1988). However, in another study, zinc supplements depressed HDL cholesterol levels and raised LDL cholesterol levels in elderly subjects (>60 years of age), especially in those who exercised. This study was not well controlled, and the wide variation in doses of the supplemented group prevented the determination of a LOAEL (Goodwin et al. 1985). Young women with a total daily intake of 1.6 mg zinc/kg/day in a 2-month study had a transient decrease in HDL cholesterol (Freeland-Graves et al. 1980). In a double-blind crossover study of young men and women receiving 2.0 (men) or 2.4 (women) mg zinc/kg/day for 6 weeks, total HDL cholesterol was not affected, and LDL cholesterol was significantly decreased in the women (Samman and Roberts 1988). No effect on HDL cholesterol was seen in elderly men and women (60-89-years old) with a total daily intake (dietary zinc plus a zinc acetate supplement) of 1.5 mg/kg/day for 3 months (Bogden et al. 1988) but the subjects also received copper supplements (about 0.03 mg/kg). Another study (Hale et al. 1988) reported no differences in triglycerides and cholesterol levels in subjects (>68-years old) given zinc supplements of up to 2 mg/kg/day for an average of 8 years.

Increases in serum cholesterol levels were observed in two studies where rats were fed either 2.8 or 10 mg zinc/kg/day as zinc acetate for 2-7 months (Katya-Katya et al. 1984; Klevay and Hyg 1973). Other studies have shown no effect on total cholesterol, HDL cholesterol, or serum

triglyceride levels in rats ingesting 3 or 2.5 mg zinc/kg/day of unspecified zinc compounds (Fischer et al. 1980; Woo et al. 1983).

Body Weight. No effects on body weight have been reported in humans following oral exposure to zinc. However, body weight gain was decreased by 46% in preruminant calves that consumed 91 mg zinc/kg/day as zinc oxide for 5 weeks; there was no effect at 64 mg zinc/kg/day (Jenkins and Hidiroglou 1991). The relevance of this effect to humans is unclear. Body weights of rabbits-(Bentley and Grubb 1991), rats (Llobet et al. 1988a), and minks (Aulerich et al. 1991) were unaffected by dosing with 174, 191, and 326.7 mg zinc/kg/day, respectively, for 3-12 months.

2.2.2.3 Immunological Effects

Zinc plays a role in the normal development and maintenance of the immune system, such as in the lymphocyte response to mitogens and as a cofactor for the thymic hormone thymulin (Delafuente 1991; Franker et al. 1986). Oral exposure to zinc at levels much higher than the RDA has impaired immune and inflammatory responses. This was observed in *in vivo* investigations of the immune competence of blood components taken from 11 healthy adult men after ingestion of 4.3 mg zinc/kg/day as zinc sulfate for 6 weeks. The mitogenic response elicited from peripheral blood lymphocytes and the chemotactic and phagocytic responses of polymorphonuclear leukocytes were impaired after zinc ingestion. No effects were seen on total numbers of lymphocytes or relative numbers of T cells, T cell subsets, or B cells (Chandra 1984). The relationship between these observations and decreased levels of immune competence that might lead to increased susceptibility to disease is unknown. Zinc supplements administered to elderly populations at doses up to 1.5 mg zinc/kg/day (Bogden et al. 1988) or 2.5 mg zinc/kg/day (Duchateau et al. 1981) resulted in either no effect or a beneficial effect on immune cell titers or delayed cutaneous hypersensitivity responses to specific antigens.

Decreased lymphocyte activity (incorporation of ^{3}H-thymidine in response to concanavalin A) was reported in mink kits from dams who had ingested a time-weighted-average dose of 20.8 mg zinc/kg/day as zinc sulfate for 10 weeks prior to conception and throughout gestation and lactation (Bleavins et al. 1983). The dose to the kits is unknown. In contrast, no effect was observed on antibody titre (immunoglobulin G [IgG] and immunoglobulin M [IgM]) or the mitogenic response of splenic B cells isolated from mice fed 76.9 mg zinc/kg/day as zinc sulfate

for 4 weeks and challenged with B cell antigens either *in vivo* or *in vitro* (Schiffer et al. 1991). The *in vitro* mitogenic response of T cells isolated from these mice was increased.

The highest NOAEL value in animals and the LOAEL value in humans for immunological effects after intermediate-duration oral exposure are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

Zinc appears to be necessary for normal brain function (Sandstead et al. 1983), but excess zinc is toxic. A 16-year-old boy who ingested ≈86 mg zinc/kg/day of metallic zinc over a 2-day period in an attempt to promote wound healing, developed signs and symptoms of lethargy, lightheadedness, staggering, and difficulty in writing clearly (Murphy 1970). Lethargy was also observed in a 2-year-old child who ingested a zinc chloride solution (≈l,000 mg zinc/kg) (Potter 1981). It is not known whether these observations represent direct effects on the nervous system.

Very limited data were located regarding neurological effects in animals. Minor neuron degeneration and proliferation of oligodendroglia occurred in rats dosed with 487 mg zinc/kg/day as zinc oxide for 10 days (Kozik et al. 1980). Rats receiving 472 mg zinc/kg/day for 10 days had increased levels of secretory material in the neurosecretory nuclei of the hypothalamus (Kozik et al. 1981).

2.2.2.5 Reproductive Effects

Pregnant women receiving capsules containing 0.3 mg zinc/kg/day as zinc sulfate during the last two trimesters did not exhibit any reproductive effects (no changes in maternal body weight gain, blood pressure, postpartum hemorrhage, or infection) (Mahomed et al. 1989). No other studies were located regarding reproductive effects in humans after oral exposure to zinc.

No measurable effect on gestational length or litter size was observed when female mink ingested a time-weighted'average dose of 20.8 mg zinc/kg/day as zinc sulfate (Bleavins et al. 1983). No histological alterations in the testes or ovaries were noted in mice fed zinc sulfate (1,110 mg zinc/kg/day) for 13 weeks (Maita et al. 1981). Male and female rats receiving 50 mg zinc/kg/day as zinc carbonate in the diet were reported to reproduce normally for several

generations in a poorly documented study by Sutton and Nelson (1937). Rats fed 250 mg zinc/kg/day for 14-17 weeks mated successfully but had a higher than normal percentage of stillborn pups A subsequent mating of the parental generation fed 2.50 mg zinc/kg/day for 5 months was unsuccessful. No reproduction occurred in rats fed 500 mg zinc/kg/day for 5 months (Sutton and Nelson 1937). The frequency of sperm with an altered chromatin structure was increased in rats fed 25 mg zinc/kg/day as zinc chloride for 8 weeks (Evenson et al. 1993). Preimplantation loss increased in rats fed diets containing 200 mg zinc/kg/day as zinc sulfate on gestational days 0-18 (Pal and Pal 1987). When the rats received 200 mg zinc/kg/day 21 days prior to mating, no effects on implantation or other adverse reproductive effects were observed (Pal and Pal 1987). The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

Zinc is necessary for normal fetal growth and development. Fetal damage may result from zinc deficiency. Only one report in the literature suggested adverse developmental effects in humans due to exposure to excessive levels of zinc (Kumar 1976). Four women were given zinc supplements of 0.6 mg zinc/kg/day as zinc sulfate during the third trimester of pregnancy. Three of the women had premature deliveries, and one delivered a stillborn infant. However, the significance of these results cannot be determined because very few details were given regarding the study protocol, reproductive histories, and the nutritional status of the women. Other human studies have found no developmental effects in the newborns of mothers consuming 0.3 mg zinc/kg/day as zinc sulfate (Mahomed et al. 1989) or zinc citrate (Simmer et al. 1991) or 0.06 mg zinc/kg/day as zinc aspartate (Kynast and Saling 1986) during the last two trimesters.

The developmental toxicity of zinc in experimental animals has been evaluated in a number of investigations. Exposure to high levels of zinc in the diet prior to and/or during gestation has been associated with increased fetal resorptions, reduced fetal weights, altered tissue concentrations of fetal iron and copper, and reduced growth in the offspring.

Administration of zinc in rats at 200 mg zinc/kg/day as zinc oxide in the diet for 21 days prior to mating and then throughout gestation resulted in resorption of all fetuses (Schlicker and Cox

1968). Fetal resorptions ranged from 4% to 29% when 200 mg zinc/kg/day was administered only during gestation (controls had no resorptions). When the dose was reduced to 100 mg zinc/kg/day starting 21 days prior to mating, there were no fetal resorptions, malformations, or growth reduction. In contrast, Kinnamon (1963) reported no resorptions, no difference in the number of offspring per litter, and no change in average wet weight of the fetuses from female rats fed 250 mg zinc/kg/day as zinc carbonate in the diet for 53 days before mating and during gestation. The reason for the differences in the results of these studies is unknown. No effect on fetal viability, size, or malformations was seen in fetuses from female rats fed 25 mg zinc/kg/day as zinc carbonate during gestational days l-18 (Uriu-Hare et al. 1989).

Administration of 200 mg zinc/kg/day to dams throughout gestation resulted in decreased growth and tissue levels of copper and iron in fetal rats (Cox et al. 1969; Schlicker and Cox 1968). In rats, at both 100 and 200 mg/kg/day during gestational days l-18, maternal zinc levels increased. However, zinc tissue levels in the 22-day-old fetuses were not elevated at 100 mg/kg/day to dams, suggesting that the placenta was able to act as a barrier to zinc at the lower dietary level. In contrast, Ketcheson et al, (1969) showed that newborn and 14-day-old rats from mothers that had consumed 100 mg/kg/day throughout gestation had elevated levels of total zinc and decreased levels of iron. It is unclear whether the longer exposure to zinc during gestation or the suckling of newborn rats prior to sacrifice may have accounted for these differences.

Animal studies suggest that exposure to very high levels of dietary zinc is associated with reduced fetal weight, alopecia, decreased hematocrit, and copper deficiency in offspring. For example, second generation mice exposed to zinc carbonate during gestation and lactation (260 mg/kg/day in the maternal diet), and then continued on that diet for 8 weeks, had reduced body weight, alopecia, and signs of copper deficiency (e.g., lowered hematocrit and occasional achromotrichia [loss of hair color]) (Mulhern et al. 1986). Similarly, mink kits from dams that ingested a timeweighted-average dose of 20.8 mg zinc/kg/day as zinc sulfate also had alopecia and achromotrichia (Bleavins et al. 1983). It is likely that the alopecia resulted from zinc-induced copper deficiency,which is known to cause alopecia in monkeys (Obeck 1978). However, no adverse effects were observed in parental mice or mink.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxicity in humans after oral exposure to zinc.

Chromosomal aberrations were detected in the bone marrow cells of mice administered 350 mg zinc/kg as zinc chloride and fed a low-calcium diet (1.1% calcium), but not when the animals were given a similar zinc dose and fed a calcium-replete diet (Deknudt and Gerber 1979). A similar effect was observed in rats exposed to 14.8 mg zinc/kg/day as zinc chlorate in drinking water (Kowalska-Wochna et al. 1988).

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

Very limited data were found regarding relationships between the ingestion of zinc and its compounds by humans and the subsequent development of cancer. One study reported an association between an excess rate of gastric cancer in the people of North Wales (Great Britain) and the high zinc-to-copper ratio (≈30:1) in the soil of household gardens (Stocks and Davies 1964). However, the inference that this excess in gastric cancer is causally associated with soil levels of zinc and copper is not consistent with another study. In a survey of cancer registry data (1954-1978) in Shipham, Somerset (Great Britain), an area that also has a high soil zinc-tocopper ratio (≈17:1), the gastric cancer incidence rate was significantly lower than the regional rate (Philipp et al. 1982). It is probable that other factors, not considered by Stocks and Davies (1964), that are associated with or coincidental to the high soil zinc-to-copper ratio confounded the results.

The carcinogenicity of zinc in experimental animals following oral exposure was evaluated by Walters and Roe (1965). The incidence of tumors was not increased in mice exposed to 951 mg zinc/kg/day as zinc sulfate in drinking water for 1 year compared to controls. However, important details regarding the study protocol were lacking including the age and sex of the mice, the number of mice at the beginning of the study, the purity of the test material, and a complete list of the organs and tissues examined at necropsy. The control mice developed intercurrent disease (ectromelia), which resulted in a number of deaths; supplementary control mice were

added to the study, but they were not concurrent controls. The number of animals in treated and control groups surviving at 1 year (study termination) was small (22-28 mice/group). The exposure period (1 year) was less than the standard bioassay period (18-24 months). There were no data in the study (e.g., survival or body weight data) to indicate that a maximum tolerated dose was achieved. These limitations reduce the sensitivity of the study by Walters and Roe (1965) to detect a carcinogenic response.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to zinc.

2.2.3.2 Systemic Effects

Zinc has been reported to promote the healing of burns and wounds when topically applied as zinc oxide or calamine lotion (Gordon et al. 1981). The mechanism by which.this occurs was not discussed by the authors. Zinc oxide contained in an occlusive zinc tape dressing reduced the inflammatory reactions in the granulation tissue of wounded rats (Wetter et al. 1986). The authors speculated that zinc acted either by a continuous release of zinc ions or by modifying components involved in the tape's adhesive properties.

No studies were located regarding respiratory, cardiovascular, gas train tes tin al, musculoskeletal, hepatic, renal, or other systemic effects in humans or animals after dermal exposure to zinc. The systemic effects observed after dermal exposure are discussed below. The NOAEL values and all LOAEL values from each reliable study for dermal effects in each species and duration category are recorded in Table 2-3.

Hematological Effects. A worker who had been employed making up zinc chloride solutions (concentrations not specified) with his hands was found to have microcytic anemia and decreased numbers of platelets (DuBray 1937).

TABLE 2-3. Levels of Significant Exposure to Zinc - Dermal

Species	Exposure duration/ frequency	System	NOAEL ($mg\ Zn/cm^2$)	LOAEL (effect) Less serious ($mg\ Zn/cm^2$)	LOAEL (effect) Serious ($mg\ Zn/cm^2$)	Reference	Form
ACUTE EXPOSURE							
Systemic							
Human	48 hr	Derm/oc	2.9			Agren 1990	oxide
Rabbit	5 d	Derm/oc	0.4			Lansdown 1991	sulfate
Rabbit	5 d	Derm/oc	16			Lansdown 1991	oxide
Rabbit	5 d	Derm/oc		7.2 (slight skin irritation - open patch test)		Lansdown 1991	acetate
		Derm/oc		7.2 (severe skin irritation - occluded patch test)			
Rabbit	5 d	Derm/oc		0.48 (severe skin irritation)		Lansdown 1991	chloride
Gn pig	5 d	Derm/oc	0.4			Lansdown 1991	sulfate
Gn pig	5 d	Derm/oc		0.48 (moderate skin irritation)		Lansdown 1991	chloride
Gn pig	5 d	Derm/oc	16			Lansdown 1991	oxide
Gn pig	5 d	Derm/oc	7.2			Lansdown 1991	acetate
Mouse	5 d	Derm/oc		0.48 (severe skin irritation)		Lansdown 1991	chloride
Mouse	5 d	Derm/oc		0.4 (slight skin irritancy)		Lansdown 1991	sulfate

TABLE 2-3. Levels of Significant Exposure to Zinc - Dermal (continued)

Species	Exposure duration/ frequency	System	NOAEL ($mg\ Zn/cm^2$)	LOAEL (effect) Less serious ($mg\ Zn/cm^2$)	LOAEL (effect) Serious ($mg\ Zn/cm^2$)	Reference	Form
Mouse	5 d	Derm/oc	16			Lansdown 1991	oxide
Mouse	5 d	Derm/oc		7.2 (moderate skin irritation)		Lansdown 1991	acetate

acetate = zinc acetate; chloride = zinc chloride; d = day(s); Derm/oc = dermal/ocular; Gn pig = guinea pig; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; oxide = zinc oxide; sulfate = zinc sulfate; Zn = zinc

No studies were located regarding hematological effects in animals after dermal exposure to zinc.

Dermal/Ocular Effects. No signs of dermal irritation were observed in humans after a 25% zinc oxide patch (2.9 mg/cm^2) was placed on the skin for 48 hours (Agren 1990). However, 14 out of 17 men who were employed in the bagging or packing of zinc oxide and whose skin was frequently covered with zinc oxide dust reported having experienced zinc oxide pox at least once (Turner 1921). The pox appeared as itchy papular-pustular eruptions in the pubic region, scrotum, inner surface of the thigh, and occasionally on the axilla and inner surface of the arms. The study author suggested that these lesions were due to clogging of glands by dust, perspiration, and bacteria when skin surfaces coated with these substances were rubbed together. In contrast, a case study of 24 workers exposed to dusts of either zinc oxide, zinc sulfide, or metallic zinc revealed only 1 worker with papular pustular lesions on the axilla and inner thighs (Batchelor et al. 1926). The difference in the results was attributed to differences in the personal hygiene of the workers in the two studies.

In a case report, accidental splashing of a soldering paste containing 30% zinc chloride into the eye of a plumber produced an immediate reduction in visual acuity, hyperemia, hemorrhaging, conjunctival swelling, cornea1 opacity, bullous keratopathy, and spotting of the lens (Houle and Grant 1973). Most symptoms disappeared after 6 weeks, but residual lens opacities persisted for over a year after the exposure. Reddened conjunctivae and lacrimation were observed in 34 persons who were exposed to extremely high concentrations of zinc chloride smoke when several smoke generators exploded in a tunnel during World War II (Evans 1945). Two of the exposed persons had cornea1 burns and four had small vesicular burns on the forehead or wrist. Zinc chloride was the major component of the smoke. However, other components such as zinc oxide, hexachloroethane, calcium silicide, the igniter, or the heat of the explosion may have contributed to the injuries that were observed.

The dermal irritancy of several zinc compounds was compared in mice, rabbits, and guinea pigs (Lansdown 1991). Of the six zinc compounds tested, zinc chloride had the greatest irritancy potential, followed by zinc acetate and zinc sulfate; no signs of irritation were observed following exposure to zinc oxide. Although zinc chloride is clearly the most irritating, the relative irritancy of zinc sulfate and zinc acetate was not determined because only one dose was tested and a different dose was used for each compound. The severe skin irritancy observed following

application of zinc chloride was characterized by parakeratosis, hyperkeratosis, inflammatory changes in the epidermis and superficial dermis, and acanthosis of the follicular epithelia (Lansdown 1991).

No studies were located regarding the following health effects in humans or animals after dermal exposure to zinc:

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Reproductive Effects
2.2.3.6 Developmental Effects
2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to zinc.

2.3 TOXICOKINETICS

There is limited information on the toxicokinetic properties of zinc following inhalation or dermal exposure. Increased zinc levels in the blood and urine of humans and in the tissue of animals after inhalation and dermal exposure to zinc, respectively, indicate that zinc is absorbed by these routes. The toxicokinetic properties of ingested zinc have been extensively studied. The absorption of zinc from the gastrointestinal tract is homeostatically regulated; under normal physiological conditions, 20-30% of ingested zinc is absorbed. Zinc uptake from the intestinal lumen involves passive diffusion and a carrier-mediated process. A number of factors influence the absorption of zinc; these include inhibitors, such as calcium, phosphorus, and dietary fiber and phytates (components of dietary fiber that may coprecipitate with zinc in the intestines), and enhancers, such as amino acids? picolinic acid, and prostaglandin E_2,. Once absorbed, zinc is widely distributed throughout the body. Zinc content is highest in muscle, bone, gastrointestinal

tract, kidney, brain, skin, lung, heart, and pancreas. In plasma, two-thirds of the zinc is bound to albumin which represents the metabolically active pool of zinc. This pool of plasma zinc is frequently referred to as loosely bound zinc because albumin has the ability to give up bound zinc to tissues. Zinc is excreted in both urine and feces.

Metal fume fever, a critical end point, was observed in workers who inhaled high levels of zinc oxide fumes or dust. The mechanism of metal fume fever has been reported to be an immune response to zinc oxide in the respiratory tract. The anemia observed in humans and animals after oral exposure to high levels of zinc could result from a zinc-induced copper deficiency. Excess levels of dietary zinc inhibit the transport of copper to the blood from either the intestinal lumen or the intestinal mucosal cell.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Quantitative studies regarding absorption of zinc and zinc compounds after inhalation exposure in humans are limited. The absorption of inhaled zinc depends on the particle size and solubility. Elevated levels of zinc have been found in the blood and urine of workers exposed to zinc oxide fumes (Hamdi 1969).

The rates or percentages of absorption of inhaled zinc in animals are not available; however, studies provide data on zinc retention in the lungs. Zinc retention values were 19.8%, 11.5%, and 4.7% in the lungs of guinea pigs, rats, and rabbits, respectively, after inhalation exposure (noseonly) to 3.5-9.1 mg zinc/m^3 as zinc oxide aerosol for 2-3 hours (Gordon et al. 1992). The aerosol had a mass median diameter of 0.17 l μm. The retention of zinc in lungs was dose related in male Wistar rats administered a single intratracheal instillation of 0-07-3.7 mg zinc/m^3 as zinc oxide (Hirano et al. 1989). A half-life of 14 hours was calculated for this experiment.

The absorption of zinc oxide fumes lead to increased levels of zinc measured in the liver, kidney, and pancreas of cats exposed to zinc oxide fumes for durations ranging from 15 minutes to 3.25 hours (Drinker and Drinker 1928). The usefulness of the study is limited because reporting was inadequate and particle size of the zinc oxide aerosol was not determined. Some inhaled

particles of zinc oxide are subject to ciliary clearance and swallowing. Thus, a portion of the inhaled zinc may ultimately be absorbed from the gastrointestinal tract.

2.3.1.2 Oral Exposure

Several studies have measured oral absorption rates of zinc in humans. Absorption ranged from 8% to 81% following short-term exposures to zinc supplements in the diet; differences in absorption are probably due to the type of diet (amount of zinc ingested, amount and kind of food eaten) (Aamodt et al. 1983; Hunt et al. 1991; Istfan et al. 1983; Reinhold et al. 1991; Sandstrom and Abrahamson 1989; Sandstrom and Cederblad 1980; Sandstrom and Sandberg 1992). For example, dietary protein facilitates zinc absorption; fractional zinc absorption ranged from 8% for low-protein rolls to 26% for high-protein rolls 3 days after individuals ingested 0.05 mg zinc/kg (Hunt et al. 1991).

Absorption of labeled zinc was 40.0-48.4% in male Wistar rats fed a diet containing 0.81 mg zinc/kg as zinc chloride or zinc carbonate (Galvez-Morros et al. 1992). Fractional absorption in immature organisms generally exceeds that in adults. In growing rats, on the basis of indirect calculation from isotope experiments, Weigand and Kirchgessner (1992) suggested surprisingly high absorption values of as much as 94.7%. It is likely that all these results were influenced by isotope exchange and do not provide estimates of net absorption.

The body's natural homeostatic mechanisms control zinc absorption from the gastrointestinal tract (Davies 1980). Persons with adequate nutritional levels of zinc absorb approximately 20-30% of all ingested zinc. Those who are zinc-deficient absorb greater proportions of administered zinc (Johnson et al. 1988; Spencer et al. 1985).

Absorption of zinc occurs from all segments of the intestine, although the largest proportion of zinc absorption occurs from the duodenum (Methfessel and Spencer 1973). The zinc absorption process includes both passive diffusion and a carrier-mediated process (Tacnet et al. 1990). The intestinal absorption of zinc appears to be a saturable carrier-mediated process at low zinc dose levels involving a cysteine-rich intestinal protein (CRIP) (Davies 1980; Gunshin et al. 1991; Hempe and Cousins 1992; Sturniolo et al. 1991). This protein binds zinc entering the intestinal cells from the lumen (Hempe and Cousins 1991). CRIP has a limited binding capacity for zinc

and becomes saturated when zinc concentration in the intestine is high. Metallothionein, a metal binding protein may contribute to zinc homeostasis at higher zinc absorption. Like several other metals, zinc can induce metallothionein production in intestinal mucosal cells (Richards and Cousins 1975). Zinc binds to metallothionein, which remains in the mucosal cells lining the gastrointestinal tract, and the bound metal is excreted from the body upon sloughing off of these cells. Although the affinity of zinc for metallothionein is relatively low, the protein may thus serve to prevent absorption of excess zinc in the body (Foulkes and McMullen 1987). Thus, absorption of zinc in rats is increased when metallothionein levels are lower (Flanagan et al. 1983). It is hypothesized that zinc entering luminal cells is associated with CRIP, and a small amount is bound to metallothionein; however, as the luminal zinc concentration increases, the proportion of cytosolic zinc associated with CRIP is decreased with a concomitant increase in zinc binding to metallothionein (Hempe and Cousins 1992). Further details on the influence of CRIP and metallothionein on zinc absorption are provided in Section 2.3.5, Mechanisms of Action.

Phytate and high phosphorus intakes in animals decrease zinc absorption. In humans, dairy products that contain both calcium and phosphorus decrease zinc absorption and plasma zinc concentration (Pecoud et al. 1975). Zinc binds to phosphate which results in coprecipitation of zinc with calcium phosphate in the intestines (Nelson et al. 1985). Dietary phytate also reduces zinc absorption. The addition of 400 pmol phytate to the diet decreased zinc absorption from 43.3±17.9% in females fed bread containing 0.02 mg zinc/kg (zinc-65 isotope) to 14.3±3.2% (Sandstrom and Sandberg 1992). Rats given diets supplemented with radiolabeled zinc and phytate excreted significantly more zinc in the feces than rats given diets supplemented with radiolabeled zinc but without phytate (Davies and Nightingale 1975). The study authors suggested that the decrease in absorption was due to the formation of zinc-phytate complexes in the intestines. Phytate also reduced reabsorption of zinc secreted into the gastrointestinal tract of humans (Sandstrom and Sandberg 1992).

Endogenous substances, such as amino acids, can influence the absorption of zinc. Complexing of zinc with amino acids generally enhances its absorption in all segments of the intestine (Wapnir and Stiel 1986). Although neither zinc nor the amino acid proline are readily absorbed in the colon, complexing of zinc with proline during an *in vivo* intestinal perfusion in rats resulted in increased zinc absorption.

Acrodermatitis enteropathica is a metabolic disorder that results in the malabsorption of zinc. However, when patients afflicted with this disorder were treated with human milk, zinc absorption was enhanced (Lombeck et al. 1975). It was reported by Evans (1980) that patients with acrodermatitis enteropathica have an impaired tryptophan metabolic pathway. Picolinic acid, a chief metabolite of tryptophan, is also a constituent of human milk. Picolinic acid is secreted by the pancreas into the intestinal lumen. A study by Boosalis et al. (1983) demonstrated that patients with pancreatic insufficiency had difficulty absorbing zinc administered as zinc sulfate. However, when these pancreatic-insufficient patients were given zinc as zinc picolinate, the extent of zinc absorption was similar to that of healthy controls. Zinc absorption may depend on the bioavailability of picolinic acid. Such a mandatory role of picolinic acid in absorption has not been confirmed (Bonewitz et al. 1982).

The addition of prostaglandin E, (PGE,) to the mucosal media of everted jejunal sacs from rats significantly increased zinc transport (Song and Adham 1979). In contrast, similar addition of prostaglandin F_2 (PGF_2) significantly decreased zinc transport. Addition of PGF_2 to the serosal side of the jejunal sacs increased the transport of zinc to the mucosal side; PGE_2 decreased the serosal to mucosal transport of zinc. The mechanism by which prostaglandins regulate zinc transport has not been established (Song et al. 1992). The limitation of the *in vitro* study is the absence of vascular perfusion and consequent trapping of metals in the submucosal tissue. Hence, studies of absorption of heavy metals, including zinc, in everted sacs have limited physiological relevance (Foulkes 1984) but may provide information useful for the design of future *in vivo* experiments.

The presence of other trace metals (e.g., mercury, cadmium, copper) may also diminish zinc transport. Section 2.6 provides detailed information on the interaction of zinc with other metals.

2.3.1.3 Dermal Exposure

Dermal absorption of zinc occurs, but its mechanism is not clearly defined. Studies are very limited regarding the absorption of zinc through the skin. Historically, zinc oxide has been used clinically to promote the healing of burns and wounds (Gordon et al. 1981). Absorption has been observed in burn patients treated with gauze dressings containing zinc oxide (Hallmans 1977)

The pH of the skin, the amount of zinc applied, and the vehicle administered with zinc all affect the absorption of zinc (Agren 1990, 1991).

Zinc chloride was also absorbed through the intact skin of the rat (Keen and Hurley 1977). Absorption of zinc sulfate was greater than zinc oxide following 4-48-hour dermal application to open wounds in Sprague-Dawley rats (Agren et al. 1991). About 12% of zinc oxide (0.25 mg zinc/cm^2) from the dressing reached the wound while 65% of zinc sulfate (0.066 mg zinc/cm^2) reached the wound. The data suggest that zinc oxide applied to wounds resulted in sustained delivery of zinc ions causing constant wound-tissue zinc levels. In contrast, zinc sulfate, being more water soluble than zinc oxide, is rapidly transferred into the blood and, therefore, caused decreased wound-tissue zinc levels (Agren et al. 1991).

2.3.2 Distribution

Zinc is one of the most abundant trace metals in humans. It is found normally in all tissues and tissue fluids and is a cofactor in over 200 enzyme systems. Together, muscle and bone contain approximately 90% of the total amount of zinc in the body (≈60% and 30%, respectively) (Wastney et al. 1986). Organs containing sizable concentrations of zinc are the liver, gastrointestinal tract, kidney, skin, lung, brain, heart, and pancreas (Bentley and Gribb 1991; Drinker and Drinker 1928; He et al. 1991; Llobet et al. 1988a). High concentrations of zinc were also detected in the prostate (Forssen 1972) retina, and sperm (Bentley and Grubb 1991). Zinc levels may vary considerably from one individual to another (Forssen 1972).

To some degree, the distribution of zinc in some tissues appears to be regulated by age (Schroeder et al. 1967). Zinc concentrations increase in the liver, pancreas, and prostate and decrease in the uterus and aorta with age. Levels in the kidneys and heart peak at approximately 40-50 years of age and then decline.

Zinc is present in blood plasma, erythrocytes, leukocytes, and platelets, but is chiefly localized within erythrocytes (of which 87% is in carbonic anhydrase, the major binding site) (Ohno et al. 1985). Zinc deficiency has been demonstrated to decrease the ability of erythrocytes to resist hemolysis *in vitro*. This finding suggests that zinc stabilizes the erythrocyte membrane. In plasma, two-thirds of the zinc is bound to albumin; the remainder is bound primarily to α_2-macroglobulin

(Bentley and Grubb 1991; Giroux et al. 1976; Wastney et al. 1986). It appears that the limited number of binding sites for zinc in plasma albumin and macroglobulin regulates the amount of zinc retained by the body (Andermann and Dietz 1982). Albumin-bound zinc has been correlated with plasma zinc levels, whereas α_2-macroglobulin shows no correlation with plasma zinc levels.

Hormones, such as the adrenocorticotrophic hormone (ACTH), appear to regulate the concentration of zinc in the liver. ACTH, secreted by the anterior pituitary gland, stimulates the secretion of glucocorticoids. Glucocorticoids, or hormones with glucocorticoid activity, have been shown *in vitro* to stimulate the net zinc uptake in cultured liver cells and at the same time activate the gene that regulates metallothionein synthesis (Failla and Cousins 1978). However, there are no *in vivo* data to support these *in vitro* findings. Metallothionein in the cells of the intestinal mucosa binds zinc, thus regulating its release into the blood.

The transfer of zinc across perfused placentas is slow; only ≈3% of maternal zinc reached the fetal compartment in 2 hours (Beer et al. 1992). The *in vitro* transfer of zinc between mother and fetus is bidirectional, with binding in the placenta (Beer et al. 1992). It is proposed that zinc uptake in the placenta involves a potassium/zinc transport system (Aslam and McArdle 1992). Newborns may also be exposed to zinc from their mothers by milk transfer of zinc during lactation (Rossowska and Nakamoto 1992).

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans after inhalation exposure to zinc. However, occupational studies provided indirect evidence that zinc may distribute to tissues to produce systemic effects (Brown 1988; Drinker et al. 1927a; Malo et al. 1990; McCord et al. 1926; Rohrs 1957; Sturgis et al. 1972).

Zinc levels in the lungs of cats peaked immediately after acute exposure to 12-61 mg zinc/kg/day as zinc oxide for approximately 3 hours and remained high for 2 days postexposure, then dropped significantly thereafter (Drinker and Drinker 1928). Levels in pancreas, liver, and kidneys increased slowly.

2.3.2.2 Oral Exposure

A single oral dose of 0.7 mg zinc/kg as zinc sulfate given to I1 individuals resulted in peak zinc levels in the plasma at 2-3 hours (Statter et al. l988; Sturniolo et al. 1991). Similarly, Neve et al. (1991) reported peak serum zinc concentration at 2.3 hours with 0.7 mg zinc/kg as zinc sulfate.

Following feeding of 191 mg zinc/kg/day as zinc acetate to rats for 3 months, increased zinc levels were significant in the heart, spleen, kidneys, liver, bone, and blood (Llobet et al. 1988a). The greatest increases were in bone (258%) and blood (520%). Elevated zinc levels were found in the kidneys and liver of mice fed 76.9 mg zinc/kg/day as zinc sulfate (Schiffer et al, 1991) or 38 mg zinc/kg/day as zinc nitrate (Cooke et al. 1990) for approximately 1 month. The kidneys and pancreas had higher zinc levels than the liver and carcass of rats fed diets containing 1.1 mg/kg/day for an unspecified duration (Weigand and Kirchgessner 1992). Newborn, young, and adult mice receiving a single oral dose of 4.6 mg zinc/kg as zinc chloride generally had the highest levels of zinc in the liver, kidneys, lungs, bone, muscle, and carcass 1 day after dosing (He et al. 1991). However, the amount of zinc in the lungs, muscle, and femur decreased with age.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to zinc. Animal data on the distribution of zinc following dermal exposure are limited. Elevated serum zinc levels occurred with the application of zinc oxide or zinc sulfate to skin wounds of Sprague-Dawley rats for 4-48 hours (Agren et al. 1991). Serum zinc level peaked at 4 hours in rats treated with zinc sulfate, while levels were slightly elevated for 48 hours in rats administered zinc oxide. The differences may be attributed to the absorbability of the zinc compounds.

2.3.3 Metabolism

Plasma provides a metabolically active transport compartment for zinc (Cousins 198.5). Zinc is most often complexed to organic ligands (existing in loosely or firmly bound fractions) rather than free in solution as metallic ion (Gordon et al. 1981). Zinc is found in diffusible or nondiffusible forms in the blood (NAS/NRC 1979). In the diffusible form, approximately two-thirds of plasma

zinc is freely exchangeable and loosely bound to albumin (Cousins 1985); the zinc-albumin complex has an association constant of about 10^6 (NAS/NRC 1979). The diffusible form of zinc also includes zinc bound to amino acids (primarily histidine and cysteine). The zinc-albumin complex is in equilibrium with the zinc-amino acid complex (Henkin 1974). The zinc-amino acid complex can be transported passively across tissue membranes to bind to proteins. An important binding protein in the kidney and liver is metallothionein, although other tissue-binding proteins may be present.

In the nondiffusible form, a small amount of circulating zinc is tightly bound to α_2-macroglobulin in the plasma (Cousins 1985). Zinc is incorporated into and dissociated from α_2-macroglobulin only in the liver (Henkin 1974). This zinc-protein complex has an association constant of $>10^{10}$ (Henkin 1974; NAS/NRC 1979). Th e zinc bound to α_2-macroglobulin is not freely exchangeable with other zinc ligands (i.e., zinc-albumin and zinc-amino acid complexes) in serum.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Information was limited regarding zinc excretion following inhalation exposure in humans. Workers exposed to zinc oxide fumes had elevated levels of zinc in the urine (Hamdi 1969) indicating that this is a route of excretion.

No studies were located regarding excretion in animals after inhalation exposure to zinc.

2.3.4.2 Oral Exposure

The principal route of excretion of ingested zinc in humans is through the intestine (Davies and Nightingale 1975; Reinhold et al. 1991; Wastney et al. 1986). Zinc loss in the body is by secretion via the gut, and the remainder occurs in the urine (Wastney et al. 1986). Fecal excretion of zinc increases as intake increases (Spencer et al. 1985). Excretion of zinc in the urine also reflects zinc intake (Wastney et al. 1986). Minor routes of elimination are saliva secretion, hair loss, and sweat (Greger and Sickles 1979; Hambidge et al. 1972; Henkin et al. 1975a; Prasad et al. 1963a;

There was a linear increase in fecal excretion of zinc in proportion to dietary intake in rats fed supplementations of 32 mg zinc/kg/day as zinc oxide for 7-42 days (Ansari et al. 1975) or 50-339 mg/kg/day for 21 days (Ansari et al. 1976). No differences in fecal excretion, total excretion, or retention of zinc were found among rats given diets containing different forms of zinc (Seal and Heaton 1983). Rats receiving 2.65 mg zinc/kg/day as zinc chloride, zinc sulfate, zinc phosphate, or zinc citrate, over a 4-day period excreted 87-98% of intake.

A study by Alexander et al. (1981) demonstrated that zinc is excreted in the bile of rats. Analysis of the bile indicated that the zinc is primarily complexed with reduced glutathione. Treatment of these rats with diethylmaleate, which conjugates with reduced glutathione and restricts its availability, depressed the biliary excretion of zinc. This depression confirms a relationship between zinc and glutathione and suggests that zinc is transferred from liver to bile by a glutathione-dependent process.

Other factors may affect zinc excretion. For example, low dietary intake of zinc or malnutrition can increase the urinary excretion of zinc. This release of zinc is a result of tissue breakdown and catabolism during starvation; and elevated urinary excretion of zinc may persist after intake levels return to normal (Spencer et al. 1976). Administration of histidine or high-protein diet may increase urinary zinc excretion; however, a corresponding increase in zinc absorption may maintain zinc balance in the body (Henkin et al. 1975b; Hunt et al. 1991).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to zinc.

2.3.5 Mechanisms of Action

The absorption of zinc from the intestine is homeostatically controlled. A study by Hempe and Cousins (1992) found that CRIP, a diffusible intracellular zinc carrier, binds zinc in the mucosa during absorption; this process appears to be saturable (Gunshin et al. 1991; Hempe and Cousins 1992; Sturniolo et al. 1991). Zinc transport in the intestinal lumen is also influenced by metallothionein which can inhibit zinc absorption by competing with CRIP for zinc (Hempe and Cousins 1992). CRIP binds about 40% of radiolabeled zinc entering the intestinal cells from the

lumen in ligated loops of the small intestine of anesthetized rats when the zinc concentration is low (5 μM), but only 14% of the radiolabel when the concentration is high (300 μM) (Hempe and Cousins 1991). These findings suggest that CRIP has a limited binding capacity for zinc and becomes saturated when zinc concentration in the intestine is high (Hempe and Cousins 1992).

High luminal zinc concentrations may damage the brush border membrane, allowing zinc to enter the cell and bind nonspecifically to cell proteins and other ligands (Cousins 1985; Hempe and Cousins 1992). Within the intestinal lumen, a number of factors appears to influence the availability of zinc for absorption. Methionine, histidine, cysteine, reduced glutathione, citrate, and prostaglandin E_2 increase the intestinal uptake of zinc (Song et al. 1992) whereas inorganic inhibitors of zinc absorption include cadmium, copper, calcium, and ferrous iron (Hamilton et al. 1978; Harford and Sarkar 1991; Ogiso et al. 1979; Spencer et al. 1992; Yoshida et al. 1993). The mechanism of inhibition has not been clearly elucidated, but it is believed to involve competition for zinc binding sites in the intestinal mucosal cells; an effect on charge distribution on the mucosal membrane has also been suggested (Foulkes 1985). The organic inhibitors, including phytate and some components of dietary fiber, are believed to complex with zinc and decrease its availability. In the mucosal cell, zinc is associated with metalloproteins, including metallothionein. The release of zinc from the intracellular protein ligands and its transfer to the blood may involve diffusion of complexes with glutathione and similar compounds (Foulkes 1993).

In the plasma, albumin is the primary carrier for zinc, with smaller amounts of zinc bound to α_2-macroglobulin and amino acids (Giroux et al. 1976). The albumin-bound zinc represents the metabolically active pool of zinc. Zinc is loosely bound in plasma, and albumin-bound zinc can readily be given up to tissues; however, the mechanisms are not fully elucidated. Zinc is initially concentrated in the liver after ingestion, and is subsequently distributed throughout the body. The liver, pancreas, bone, kidney, and muscle are the major tissue storage sites. When plasma zinc levels are high, liver metallothionein synthesis is stimulated, which facilitates the retention of zinc by hepatocytes (Richards and Cousins 1975). A storage form of zinc has not been identified in soft tissues, with the possible exception of zinc metallothionein. Zinc in bone is relatively unavailable for use by other tissues.

Metal fume fever is the primary effect observed in workers exposed to zinc oxide fumes or dust (Blanc et al. 1991; Brown 1988; Drinker et al. 1927b; Vogelmeier et al. 1987). Metal fume fever

usually occurs 3-10 hours after exposure, and the symptoms persist for 24-48 hours. The exact pathogenesis of metal fume fever is not known It is believed to be an immune response to the inhaled zinc oxide (Mueller and Seger 1985). It has been suggested that the zinc oxide causes inflammation of the respiratory tract and the release of histamine or histamine-like substances. In response, an allergen-antibody complex is formed that may elicit an allergic reaction upon subsequent exposure to the allergen. In response to the allergen-antibody complex, an antiantibody is formed. The anti-antibody dominates with continued exposure to the zinc oxide, thereby producing a tolerance. When the exposure is interrupted and re-exposure occurs, the allergen-antibody complex dominates, producing an allergic reaction and symptoms of metal fume fever (McCord 1960).

Oral exposure to high levels of zinc has caused anemia, decreased levels of HDL cholesterol, and pancreatic damage in humans (Black et al. 1988; Chandra 1984; Chobanian 1981; Hooper et al. 1980; Murphy 1970) and animals (Allen et al. 1983; Aughey et al. 1977; Drinker et al. 1927d; Katya-Katya et al. 1984; Klevay and Hyg 1973; Maita et al. 1981; Straube et al. 1980). The mechanisms involved in the pancreatic damage have not been elucidated. The anemia and possibly the decreased HDL cholesterol levels are thought to be caused by a zinc-induced copper deficiency. Although it is generally accepted that the anemia is the result of copper deficiency, the relationship between zinc and copper levels and HDL cholesterol levels has been extensively debated (Fischer et al. 1980; Katya-Katya et al. 1984; Klevay and Hyg 1973; Murthy and Petering 1976) and is beyond the scope of this profile.

2.4 RELEVANCE TO PUBLIC HEALTH

Zinc is required for normal growth, bone formation, brain development, behavioral response, reproduction, fetal development, sensory function (taste and smell), immune function, membrane stability, and wound healing. The recommended dietary allowance for zinc is 5 mg/day for infants (0-l year), 10 mg/day for children (l-10 years), 15 mg/day for males (11-15 + years), 12 mg/day for females (11-15 + years), 15 mg/day for pregnant women, 19 mg/day during the first 6 months of lactation, and 16 mg/day during the next 6 months of lactation (NAS/NRC 1989b). There are over 100 enzymes that require zinc for maximum catalytic activity (Cousins 1985). Zinc provides structural integrity to the enzyme and/or participates directly in catalysis. Not all of the zinc enzymes are responsive to changes in zinc intake (Kirchgessner et al. 1976). Decreases in plasma

alkaline phosphatase, alcohol dehydrogenase, connective tissue thymidine kinase, pancreatic carboxypeptidase A, and liver nuclear DNA-dependent RNA polymerase have been observed during deficiency. No changes in carbonic anhydrase, lactate dehydrogenase, or malate dehydrogenase activities were observed.

Zinc deficiency has been observed in the inhabitants of Middle Eastern countries who have diets rich in cereals that provide little readily available zinc and who have a high incidence of parasitic infections, geophagia, and chronic infectious diseases (Prasad et al. 1963a, 1963b). The primary effects observed in males were growth failure, delayed sexual maturation, and iron-deficiency anemia (Prasad et al. 1963b). Marginal zinc deficiency has been observed in the United States (Hambidge et al. 1972; Henkin et al. 1976). Signs of deficiency include poor growth, anorexia, hypogeusia, and dysgeusia. Supplementation with zinc reversed these signs. Impaired fetal development, delayed wound healing, oligospermia, decreased serum testosterone concentration, hyperammonemia, impaired immune function, psoriasis, and decreased lean body mass have been observed in humans with experimentally induced marginal zinc deficiency (Prasad 1991) or with secondary zinc deficiency due to malabsorption, sickle cell anemia (Cunningham-Rundles et al. 1990) or cirrhosis of the liver (Parodi et al. 1991).

Metal fume fever has been observed in humans who inhaled high concentrations of zinc oxide fumes. Metal fume fever is believed to be an immune response characterized by increased body temperature, impaired lung function, increased number of leukocytes in the blood, and bronchoalveolar lavage fluid. Similar effects were observed in animals. Metal fume fever has been observed after acute, intermediate, and chronic inhalation exposures to zinc oxide.

The principal effects observed in humans after oral acute doses of zinc oxide include abdominal pain, vomiting, anemia, and pancreatic damage. The dose associated with these effects is >10-fold higher than the RDA for zinc. Similar effects are observed in animals. Kidney damage has also been observed in animals following intermediate exposure, but not in humans.

There is limited information on the dermal toxicity of zinc. Dermal application of zinc acetate, zinc chloride, or zinc sulfate caused slight-to-severe skin irritation in rabbits, guinea pigs, and mice. These compounds would also be irritating to human skin. In contrast, dermal exposure to zinc oxide did not usually cause skin irritation to humans and animals. However, a few workers

who routinely became covered with zinc oxide dust have had pustules on the axilla and inner thighs possibly formed in response to plugging of glands by sweat, bacteria, and zinc oxide dust.

Four cases of premature deliveries and stillborns were reported following supplemental oral doses of 0.6 mg zinc/kg/day during the last trimester of pregnancy in humans. Increased fetal resorptions and stillbirths were observed in rats fed diets containing ≥200 mg zinc/kg/day. Rats failed to reproduce after being fed 250 mg zinc/kg/day for 5 months. It is not known if this would also occur in humans. Positive genotoxic results have been observed *in vivo* and *in vitro* in mammalian cells. There are limited human and animal data suggesting that zinc is not carcinogenic, but more information is needed to further assess this inference.

Following ingestion of large amounts of zinc, increased levels are found in the heart, spleen, kidneys, liver, bone, and blood. It is not known if there is a relationship between the toxic effects observed in humans and tissue storage levels of zinc. Zinc stored in bone is not readily available to the general metabolic pool. During decreased calcium intake or bone resorption, zinc is released from the bone. It is not known if there are any toxic effects associated with this release of zinc.

The general population is primarily exposed to zinc by ingestion. Several factors influence the potential for adverse health effects after oral exposure to zinc, including age, gender, and diet. It is possible that people living near a hazardous waste site would be exposed to increased levels of zinc in the drinking water. This, in addition to the zinc naturally occurring in food, may result in toxic effects. Inhalation exposure to the general population is less likely because ambient air levels of zinc are generally very low; however, near a smelter, levels can be as high as 5 $\mu g/m^3$. Zinc dust from contaminated soil may also be inhaled. It is not likely that exposure to this level of airborne zinc would result in toxic effects. Dermal exposure may occur from skin contact with contaminated soil containing zinc.

Minimal Risk Levels for Zinc

Inhalation MRL's

No inhalation MRLs have been derived for zinc (see Table 2-l and Figure 2-l). A number of acute-duration human studies have identified metal fume fever as an end point of concern. Animal studies corroborate the effects observed in humans; however, other possible targets of toxicity were not examined. Only one intermediate-duration inhalation study in humans was located. In this study, no exposure levels were reported; thus, the study could not be used as the basis for the derivation of an intermediate-duration MRL. No exposure-related effects on lung function were observed in a group of welders chronically exposed to zinc; however, the exposure level was not reported. Thus, no chronic-duration inhalation MRL could be derived.

Oral MRLs

- An MRL of 0.3 mg zinc/kg/day has been derived for intermediate oral exposure to zinc. The MRL was based on hematological effects, specifically decreased hematocrit, serum ferritin, and erythrocyte superoxide dismutase activity, in women given daily supplements of 50 mg zinc as zinc gluconate for 10 weeks (Yadrick et al. 1989). The LOAEL of 1 mg/kg/day was derived from 9.72 mg zinc/day, the estimation of dietary zinc for females (20-30 years old) from the FDA Total Diet study for 1982-1986 (Pennington et al. 1989) plus 50 mg zinc/day, the reported supplemental zinc dose. A reduction in erythrocyte superoxide dismutase activity was also seen in males receiving daily zinc supplements of 50 mg for 6 weeks (Fisher et al. 1984). Zinc supplementation has been shown to decrease HDL levels with daily doses of at least 50 mg zinc for 12 weeks (Black et al. 1988; Chandra et al. 1984; Hooper et al. 1980). These studies suggest that there is a dose-response trend and that 50 mg/day is the threshold LOAEL for zinc. In animals, decreased hematocrit has been observed at higher doses (Jenkins and Hidiroglou 1991; Maita et al. 1981; Smith and Larson 1946).

- The intermediate oral MRL of 0.3 mg zinc/kg/day has been adopted as the chronic oral MRL. The chronic oral MRL is expected to be without adverse effects when consumed on a daily basis over a long period of time; neither inducing nutritional deficiency in healthy,

non-pregnant, adult humans ingesting the average American diet nor causing undesirable inhibition of normal lipid transport. The MRL was not based on a chronic-duration oral study due to a lack of adequate long-term studies in humans and animals. The chronic human study by Hale et al. (1988) provides support for the Yadrick et al. (1989) study and suggests that hematological effects may occur at higher zinc doses. A significant decrease in red blood cells in females receiving daily supplements of 2 mg zinc/kg/day for an average of 8 years was reported by Hale et al. (1988). Furthermore, decreases in serum creatinine, total protein, and uric acid and an increase in mean MCH were observed in the treated male and female subjects (mean age of 78 years) compared to controls.

In general, the MRL is an estimate of the daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. The intermediate and chronic oral MRLs for zinc do not provide levels of concern for zinc in infants, children, or lactating women. Also, the MRLs are based on soluble zinc salts, and it is less likely that nonsoluble zinc compounds would have these effects at this level.

No oral acute MRL was derived for zinc (see Table 2-2 and Figure 2-2). A number of case reports involving acute exposure were located. These reports suggest that the gastrointestinal tract and the pancreas are end points of concern, and that the adrenal cortex may also be affected. A great deal of uncertainty exists regarding the exposure levels for these studies. An oral exposure study in sheep was also identified. Because sheep are ruminants, it is doubtful that they are a good model for human toxicity.

Death. Death from respiratory failure has occurred in humans after acute inhalation exposure to zinc chloride smoke (Evans 1945; Hjortso et al. 1988; Milliken et al. 1963). However, the level of airborne zinc was not determined. Furthermore, exposure to zinc was accompanied by exposure to other chemicals. Hence, death could not be attributed exclusively to zinc exposure.

Only limited information was located regarding death in animals from inhalation exposure to zinc. The LCT_{50} of zinc chloride was reported as 11,800 mg-min/m^3 (Schenker et al. 1981), but the basis for this value was not provided. Exposure to 119.3-121.7 mg zinc/m^3 as zinc chloride smoke for 3-20 weeks decreased the survival of guinea pigs and mice (Man-s et al. 1988). Death was

reported in ferrets orally exposed to 390 mg zinc/kg/day as zinc oxide (Straube et al. 1980) and mice exposed to 1,110 mg zinc/kg/day as zinc sulfate (Maita et al. 1981) following acute and intermediate oral exposures, respectively. Adverse systemic effects were observed in these animals, but the specific cause of death could not be determined. Acute oral LD50 values in rats depend on the specific zinc compound and range from 237 mg zinc/kg as zinc acetate to 623 mg zinc/kg as zinc sulfate. In mice, the range of LD_{50} values is 86 mg zinc/kg as zinc acetate to 605 mg zinc/kg as zinc chloride (Domingo et al. 1988a). Death from exposure to environmental levels of zinc is improbable.

Systemic Effects

Respiratory Effects. Respiratory disorders have been observed in humans and animals after acute inhalation exposure to zinc and its compounds. No adverse respiratory effects have been observed following ingestion or dermal application of zinc or its compounds.

Acute exposure to high concentrations of airborne zinc oxide in humans causes metal fume fever. Zinc oxide penetrates the alveoli, damages the lung tissue, and transiently impairs pulmonary function (Blanc et al. 1991; Brown 1988; Drinker et al. 1927b; Vogelmeier et al. 1987). Lung volumes are decreased, as is the carbon monoxide diffusion capacity (Drinker et al. 1927b; Mueller and Seger 1985; Sturgis et al. 1927). Metal fume fever is believed to be the result of an immune reaction to inhaled metal oxide particles (Mueller and Seger 1985).

Respiratory tract irritation occurs in both humans and animals (Drinker and Drinker 1928; Sturgis et al. 1927) after exposure to zinc oxide. Most laboratory animals, except guinea pigs, begin to present respiratory abnormalities (e.g., pulmonary congestion, peribronchial leukocytic infiltration) at exposure levels similar to those that cause effects in humans (Drinker and Drinker 1928). Cats exhibited more severe effects, including bronchopneumonia, than other animals (Drinker and Drinker 1928).

In humans, inhalation of zinc chloride causes greater damage to respiratory tissue than inhalation of zinc oxide. Reported lesions included acute pneumonitis, ulceration of mucous membranes, subpleural hemorrhage, and pulmonary fibrosis. Exposed individuals have died from respiratory

distress syndrome (Evans 1945; Hjortso et al. 1988; Johnson and Stonehill 1961; Matarese and Matthews 1966; Milliken et al. 1963; Schenker et al. 1981).

The studies in humans and animals reveal that inhalation of zinc as particulate or fume can result in respiratory ailments (Drinker and Drinker 1928; Sturgis et al. 1927). These zinc fumes or particles are a particular problem for industrial workers. It is possible that inhalation exposure to zinc compounds could result in respiratory effects in people living near a hazardous waste site.

Cardiovascular Effects. In humans, oral exposure of intermediate duration to zinc has decreased serum HDL cholesterol levels (Chandra 1984; Hooper et al. 1980). Although this is not a direct effect on the cardiovascular system, the decrease in HDL levels may be associated with an increased risk of coronary artery disease. However, another study showed no effect on HDL levels and a decrease in LDL levels (Samman and Roberts 19&S), which would be associated with a decreased risk of coronary artery disease. More information on this effect is presented later in this section under Other Systemic Effects. It is not known if exposure to zinc in air, water, or soil would result in cardiovascular effects in people living near hazardous waste sites.

Gastrointestinal Effects. Gastrointestinal irritation (abdominal pain, vomiting, nausea, esophageal erosions, and gastric hemorrhagic erosion) has been observed in humans after acute ingestion of zinc compounds. In most cases, the actual exposure levels associated with these effects are not known (Anonymous 1983; Chobanian 1981; Potter 1981). In a 15year-old girl, epigastric discomfort, gastritis, and hemorrhagic erosion were observed after exposure to 2.6 mg zinc/kg/day as zinc sulfate for 1 week (Moore 1978). Longer-term human oral studies found no signs of gastrointestinal irritation at dose levels of ≤4.3 mg zinc/kg/day (Chandra 1984; Hallbook and Lanner 1972; Hoffman et al. 1988; Hooper et al. 1980; Shah et al. 1988). Gastrointestinal effects were not investigated in human inhalation studies. One mechanism for clearing particles (≥3 pm in diameter) from the respiratory tract is swallowing. It is possible, therefore, that exposure to airborne zinc would result in gastrointestinal effects. Ulceration of the forestomach and intestinal hemorrhages have been observed in mice ingesting 1,110 mg zinc/kg/day as zinc sulfate and ferrets consuming 390 mg zinc/kg/day as zinc oxide, respectively (Maita et al. 1981; Straube et al. 1980). Gastrointestinal irritation could occur in humans exposed to zinc in air, water, or soil near hazardous waste sites.

Hematological Effect. In humans, oral chronic exposure to high levels of zinc caused decreased levels of hemoglobin and hematocrit, and/or microcytic anemia (Broun et al. 1990; Hale et al. 1988; Hoffman et al. 1988; Patterson et al. 1985; Porter et al. 1977; Prasad et al. 1978). Reduction in serum ferritin and erythrocyte superoxide dismutase activity in humans have also been reported in intermediate-duration studies (Fischer et al. 1984; Yadrick et al. 1989). Similar effects have been observed in rats (Maita et al. 1981), mice (Maita et al. 1981; Walters and Roe 1965), rabbits (Bentley and Grubb 1991), dogs (Drinker et al. 1927d), ferrets (Straube et al. 1980), and preruminant calves (Jenkins and Hidiroglou 1991). The anemia is believed to be the result of zinc-induced copper deficiency. *De novo* synthesis of metallothionein in the intestinal mucosal cells is induced by high levels of dietary zinc (Cousins 1985). Copper has a higher binding affinity than zinc to metallothionein and will replace the zinc. Metallothionein-bound copper is not transferred to the portal blood and is excreted in the feces when the intestinal mucosal cell is sloughed off (Fischer et al. 1981; L'Abbe and Fischer 1984a). Decreases in hemoglobin and hematocrit levels were larger in animals fed diets low in copper and high in zinc, compared to those fed a diet with adequate levels of zinc but low levels of copper, or those fed a diet with excess zinc but adequate levels of copper (Johnson and Flagg 1986). Although the interaction between copper and zinc has been well established in animals, conflicting results have been observed in human studies. Copper deficiency has been diagnosed in individuals chronically (14-24 months) taking zinc sulfate for the treatment of sickle-cell anemia or celiac disease (Porter et al. 1977; Prasad et al. 1978). Studies have also reported increases in fecal excretion of copper and decreased copper retention in healthy subjects consuming high levels of zinc (Burke et al. 1981; Festa et al. 1985; Greger et al. 1978a). Other studies in humans have not reported altered copper metabolism (Colin et al. 1983; Greger et al. 1978b; Henkin et al. 1976; Samman and Roberts 1987; Taper et al. 1980). Anemia might occur in humans if exposed orally to zinc found near hazardous waste sites.

Leukocytosis has been reported in a number of studies of acute human exposure to zinc oxide fumes (Brown 1988; Drinker et al. 1927a; Malo et al. 1990; Mueller and Seger 1985; Rohrs 1957; Sturgis et al. 1927). Data are contradictory regarding whether inhalation exposure of humans to zinc oxide can result in anemia (Hamdi 1969; McCord et al. 1926), and very limited human data suggest that dermal exposure to zinc chloride perhaps could cause anemia (DuBray 1937). None of the animal inhalation or dermal exposure studies examined hematological parameters. Altered copper metabolism has not been observed following subcutaneous administration of zinc in rats

(Hill et al. 1984). The limited data suggest that anemia might occur in humans exposed to zinc by inhalation or dermally near hazardous waste sites.

Musculoskeletal Effects. Musculoskeletal effects have not been observed in humans or animals after inhalation, oral, or dermal exposure to zinc or its compounds. Muscles and bones contain the highest levels of zinc, and bones are believed to serve as storage depots for zinc. It is not known whether high levels of zinc in bone might be a problem because of replacement of other minerals in the bone.

Hepatic Effects. Hepatic effects have not been observed in humans after inhalation, oral, or dermal exposure to zinc. Hepatic necrosis was observed in sheep after acute and intermediate exposures to zinc compounds (Allen et al. 1983). Intermediate oral exposure of rats to zinc compounds induced liver enzymes at a dose similar to that administered to sheep (Kadiiska et al. 1985). No histopathological alterations have been observed in the livers of rats (Drinker et al. 1927c; Kadiiska et al. 1985; Llobet et al. 1988a) or mink (Aulerich et al. 1991) after intermediateduration ral exposure to zinc. The weight of evidence suggests that the liver is not a primary target organ in humans or animals for zinc toxicity.

Renal Effects. No adverse renal effects have been observed in humans after inhalation or oral exposure to zinc compounds. Following intermediate oral exposure to zinc compounds, cellular damage in the glomerulus and proximal convoluted tubules and regressive lesions were observed in rats and mice (Llobet et al. 1988a; Maita et al. 1981). It is not known whether renal effects may be found in humans living near a hazardous waste site where zinc is present in the air, water, or soil.

Dermal/Ocular Effects. Adverse dermal or ocular effects have not been observed in humans after inhalation or oral exposure to zinc. When applied to the skin, zinc's effects differ with respect to the particular zinc salt. Zinc oxide creams are widely used to promote wound healing. No signs of skin irritation were observed in humans after dermal exposure to zinc oxide (Agren 1990). Intermediate to chronic exposure to high concentrations of zinc oxide dust has resulted in plugging and infection of the sebaceous glands on the axilla and inner thighs and in the pubic region (Batchelor et al. 1926; Turner 1921). It was reported that this effect was probably due to poor hygiene rather than the irritancy of the zinc oxide dust. In contrast, zinc chloride was

reported to be irritating to the eyes and skin at very high concentrations. Exposure to extremely high concentrations of zinc chloride-containing smoke resulted in reddened conjunctiva and running eyes in 34 persons, cornea1 burns in 2 persons, and small burns on the forehead or wrists of 4 persons (Evans 1945). In rabbits, guinea pigs, and mice, moderate-to-severe skin irritation was observed following dermal exposure to zinc acetate or zinc chloride. Slight irritation in mice, but no irritation in rabbits or guinea pigs, was observed after exposure to zinc sulfate; no signs of skin irritation were observed in rabbits, guinea pigs, or mice following application of zinc oxide (Lansdown 1991). Exposure to air or water at or near a hazardous waste site containing a sufficiently high concentration of one of the more caustic zinc salts could result in skin or eye irritation.

Other Systemic Effects. Elevated body temperature, a symptom of metal fume fever syndrome, was reported by workers inhaling zinc fumes and dust (Malo et al. 1990).

Systemic effects observed in humans and animals after oral exposure to zinc compounds include damage to the pancreas and adrenal gland, alterations in the serum lipid profile, and pituitary hyperactivity. An increase in serum amylase and lipase levels was observed in individuals ingesting single high-level doses of zinc (Chobanian 1981; Murphy 1970). These changes are indicative of pancreatic damage. Pancreatic lesions have been observed in rats (Maita et al. 1981) mice (Aughey et al. 1977; Maita et al. 1981) cats (Drinker et al. 1927d), ferrets (Straube et al. 1980) and sheep (Allen et al. 1983) after intermediate or chronic oral exposure to high levels of zinc compounds. Several of the intermediate-duration studies reported that the lesions were located in the acinar cells. Acinar cell necrosis and metaplasia in pancreas were reported in rats exposed to 565 mg/kg/day and mice exposed to 1110 mg/kg/day in an intermediate-duration study (Maita et al. 1981). The pancreatic acinar cells are responsible for the secretion of pancreatic lipase, pancreatic amylase, trypsinogen, chymotrypsinogen, and procarboxypeptidase. A chronic mouse study reported marked cellular alterations in the pancreatic islets during 12 months of oral exposure to 70 mg/kg/day (Aughey et al. 1977). The islets are involved in the secretion of insulin and glucagon. No changes in blood glucose or insulin levels and no change in the response to a glucose load were observed in humans after a single dose of 0.5 mg zinc/kg/day as zinc sulfate (Brandao-Neto et al. 1990b).

Decreases in serum cortisol levels in humans after a single oral dose of zinc sulfate may indicate adrenal cortical damage (Brandao-Neto et al. 1990a). A chronic-duration drinking water study in rats exposed to 70 mg/kg/day revealed hypertrophy and vacuolation of the zona fasciculata cells of the adrenal cortex (Aughey et al. 1977). Glucocorticoids (cortisol, cortisone, corticosterone, deoxycorticosterone) are secreted by cells in the zona fasciculata. It is not known if there is a relationship between the damage to the pancreatic islets and the hypertrophy of the zona fasciculata cells in the adrenal cortex.

Decreased levels of serum HDL cholesterol were observed in humans after oral exposure to high levels of zinc for an intermediate duration (Black et al. 1988; Chandra 1984; Hooper et al. 1980). No other consistent changes in the serum lipid profile (total cholesterol, LDL cholesterol, and triglyceride levels) were observed. Changes in HDL cholesterol were not observed in young subjects (mean age of 22 years) (Samman and Robetts 1988) or in elderly subjects (60-89-years old) who also received copper supplements for 3-12 months (Bogden et al. 1988). Increases in serum cholesterol have been observed in rats in some oral exposure studies (Katya-Katya et al. 1984; Klevay and Hyg 1973). However, other studies using similar zinc compounds, doses, and durations of exposure have not found alterations in the serum lipid profile of rats (Fischer et al. 1980; Woo et al. 1983). It is possible that inhalation, oral, or dermal exposure to zinc compounds at hazardous waste sites could cause pancreatic damage, adrenal gland damage, and an alteration in the serum lipid profile.

Immunological Effects. Although the pathogenesis of metal fume fever is uncertain, it is believed to be an immune response to submicron-sized particles of zinc oxide. In addition, increased levels of lymphocytes, polymorphonuclear leukocytes, and macrophages were observed in the bronchoalveolar lavage fluid of welders. Significant correlations between the concentration of airborne zinc and the levels of T cells were reported by Blanc et al. (1991). Impaired immune function was also observed in humans taking high-dose (4.3 mg zinc/kg/day) zinc sulfate supplements for 6 weeks (Chandra 1984). Immunotoxicity was not observed in mice after oral exposure to 76.9 mg zinc/kg/day as zinc sulfate for 4 weeks (Schiffer et al. 1991). Immune suppression was observed in rats given a single injection of zinc chloride (82 mg zinc/kg) (Yatsuyanagi et al. 1987). Because zinc particles flocculate in the atmosphere, it is unlikely that persons near hazardous waste sites would be exposed to zinc particles fine enough (≤1 μm in diameter) to enter the alveolar region of the lung and elicit an immune response. However,

ingestion of zinc in drinking water at concentrations found at hazardous waste sites could result in immune suppression.

Neurological Effects. Zinc appears to be necessary for normal brain function. Nonspecific signs and symptoms of neurotoxicity (headache, dizziness, lethargy, staggering gait) have been observed in humans after acute ingestion of large amounts of zinc compounds (Anonymous 1983; Murphy 1970; Potter 1981). Neurotoxicity has not been observed in animals after inhalation, oral, or dermal exposure to zinc or its compounds although minor neuron degeneration was observed in rats after a 10-day oral exposure (Kozik et al. 1988). *In vitro* investigations on the effects of zinc on neurological tissue indicate that zinc competitively inhibits the entry of calcium into nerve terminals, thereby influencing the release of neurotransmitters (Nishimura 1987). Zinc (at concentrations that may occur *in vivo*) is toxic to neurons and glial cells of the central nervous system *in vitro* cultures (Choi et al. 1988; Yokoyama et al. 1986). It is not known if neurological effects would occur in humans exposed to zinc in air, water, or soil at or near a hazardous waste site.

Reproductive Effects. Daily oral exposure to zinc sulfide to women during the last two trimesters did not cause any complications in pregnancies (Mahomed et al. 1989). No studies were located regarding reproductive toxicity in humans after inhalation or dermal exposure to high levels of zinc. Zinc deficiency in humans has been shown to result in abnormalities of labor, atonic bleeding, pre-term labor, and post-term pregnancies.

Oral exposure to high levels of zinc increased the incidence of pre-implantation loss in rats when exposure began on gestational day 0 and continued throughout the gestational period (Pal and Pal 1987). Failure to reproduce was observed in multiparous rats fed 250 mg zinc/kg/day as zinc carbonate for 150 days. In rats fed zinc for 21 days prior to mating, no reproductive effects were observed (Pal and Pal 1987). No histological alterations of the testes or ovaries were observed in rats and mice fed high levels of zinc in their diet (Maita et al. 1981). There are very limited data to suggest that reproductive effects might occur in humans exposed to zinc in air, water, or soil at or near a hazardous waste site.

Developmental Effects. There is only one report of developmental effects occurring in humans exposed to high levels of zinc compounds. In this brief report, three cases of stillbirths and one

case of premature delivery were observed in a group of women taking 0.6 mg zinc/kg/day as zinc sulfate supplements during the third trimester of pregnancy (Kumar 1976). Extreme caution must be taken in interpreting the results of this study. The number of subjects taking the supplements, demographic information on the women, and comparison of the exposed individuals to a unexposed control group were not reported. A number of other human studies found no developmental effects in the children of mothers taking zinc supplements (highest NOAEL is 0.3 g zinc/kg/day) (Kynast and Saling 1986; Mahomed et al. 1989; Simmer et al. 1991). Zinc deficiency in humans is associated with pregnancy complications, particularly growth retardation.

An increase in the incidence of fetal resorptions and decreased fetal weights were observed in rats after oral exposure to 200 mg zinc/kg/day prior to and during mating and throughout gestation (Schlicker and Cox 1968). Alopecia and hair discoloration were observed in the offspring of mice exposed to 260 mg zinc/kg/day (Mulhern et al. 1986). These effects are believed to be the result of zinc-induced copper deficiency. No developmental effects were observed in rats exposed to up to 100 mg zinc/kg/day (Schlicker and Cox 1968; Uriu-Hare et al. 1989).

Congenital malformations, such as exencephaly and rib fusions, have been observed in the offspring of pregnant golden hamsters injected intravenously with a single dose of 2 mg zinc sulfate/kg on day 8 of gestation (Ferm and Carpenter 1968). Similarly, single intraperitoneal injections of 12.5, 20.5, or 25 mg/kg zinc chloride on days 8, 9, 10, or 11 of gestation produced skeletal anomalies, including delayed ossification and rippled ribs without accompanying soft tissue defects in mice. Rippled ribs, an unusual anomaly, appeared when zinc salt was given on day 9 of gestation at a dose of 20.5 mg/kg, becoming more prevalent when 25 mg/kg of the salt was administered on day 11 of gestation (Chang et al. 1977). It is not known whether exposure to air, waker, or soil at or near a hazardous waste site could cause developmental effects in humans.

Genotoxic Effects. Genotoxicity studies conducted in a variety of test systems have failed to provide evidence for mutagenicity of zinc. However, there are indications of weak clastogenic effects following zinc exposure.

Results of *in vivo* studies are shown in Table 2-4. A dominant lethal study in mice failed to show a mutagenic potential for zinc. However, chromosomal aberrations have been observed in bone

TABLE 2-4. Genotoxicity of Zinc *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian systems:			
Mouse	Dominant lethal	-	Vilkina et al. 1978
Mouse bone marrow	Chromosomal	+	DeKnudt and Gerber 1979
Mouse	Chromosomal	+	Voroshilin et al. 1978
Rat bone marrow	Chromosomal aberrations	+	Kowalska-Wachna 1988
Mouse bone marrow	Chromosomal aberrations	+	Gupta et al. 1991
Rat bone marrow	Sister chromatid exchange	+	Kowalska-Wachna 1988
Mouse	Micronucleus	-	Gocke et al. 1981
Drosophila	Sex-linked recessive lethal	-	Gocke et al. 1981

- = negative result; + = positive result

marrow cells following *in vivo* exposure to zinc (Vilkina et al. 1978). This effect was observed in rats exposed to 14.8 mg zinc/kg/day as zinc chlorate in drinking water (Kowalska-Wochna et al. 19&Q mice given intraperitoneal injections of 3.6 mg zinc/kg/day as zinc chloride (Gupta et al. 1991), and mice exposed to zinc oxide by inhalation (Voroshilin et al. .1978). Chromosomal aberrations caused by zinc were observed in the bone marrow cells of mice maintained on a low-calcium diet (Deknudt and Gerber 1979). Calcium may be displaced by zinc in calcium-depleted conditions, leading to chromosome breaks and/or interfering in the repair process (Deknudt and Gerber 1979). An increased incidence of sister chromatid exchange was observed in bone marrow cells of rats exposed to 17.5 mg zinc/kg/day as zinc chlorate in drinking water (Kowalska-Wochna et al. 1988).

Results of *in vitro* studies are shown in Table 2-5. Exposure to zinc as zinc sulfate or zinc chloride does not increase mutation frequencies in bacterial or mammalian cell culture test systems (Amacher and Paillet 1980; Gocke et al. 1981; Marzin and Vo Phi 1985; Nishioka 1975; Thompson et al. 1989; Venitt and Levy 1974; Wong 19&S). Similarly, there was no convincing evidence of a clastogenic effect in human lymphocytes exposed to 0.0003-0.00003 M zinc chloride (Deknudt and Deminatti 1978).

Cancer. No reliable human carcinogenicity data were located. The carcinogenicity of zinc following oral exposure has been evaluated in a study with mice (Walters and Roe 1965). In this study, mice were given 0, 190, or 951 mg zinc/kg/day as zinc sulfate in drinking water for 1 year. Relative to controls, no increase in tumor incidence was observed in treated mice. The investigation was not adequate for evaluating the carcinogenicity of zinc because of several study limitations (inadequate or lack of details of protocol, age, sex, number of animals tested, and purity of test material). Lung adenomas were not found in mice injected intraperitoneally with doses up to 5.3 mg/kg/day, three times a week, for 8 weeks (Stoner et al. 1976), but there was no indication that a sufficiently high dose was tested. Teratomas of the testes were observed in fowl given testicular injections of 2 mL of a 10% zinc sulfate solution (Falin and Gromzewa 1939) but they were not observed in rats given testicular injections of 23 mg zinc/kg/day as zinc sulfate (Guthrie 1956). The relevance of this study to public health is not known. EPA has determined that zinc is not classifiable as to its human carcinogenicity (IRIS 1993).

TABLE 2-5. Genotoxicity of Zinc *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (TA102)	Gene mutation	Not tested	-	Marzin and Vo Phi 1985
S. typhimurium (TA98, TA102, TA1535, TA1537)	Gene mutation	-(S9)	-	Wong et al. 1988
S. typhimurium (TA1538, TA98, TA100, TA1537)	Gene mutation	-(S9)	-	Thompson et al. 1989
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutation	-(S9)	-	Gocke et al. 1981
Escherichia coli	Gene mutation	Not tested	-	Nishioka 1975
E. coli	Gene mutation	Not tested	-	Venitt and Levy 1974
Mammalian cells:				
Mouse lymphoma	Gene mutation	Not tested	-	Amacher and Paillet 1980
Mouse lymphoma	Gene mutation	+(S9)	+	Thompson et al. 1989
Human lymphocytes	Chromosomal aberrations	Not tested	+	Deknudt and Deminatti 1978
Chinese hamster ovary cells	Chromosomal aberrations	+(S9)	+	Thompson et al. 1989

- = negative result; + = positive result

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAWNRC 1989a).

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989a). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to zinc are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989a). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by zinc are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an

intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Zinc

There is no simple measure of zinc body burden. Under normal physiological conditions, the plasma/serum zinc level is ≈1 μg/mL (NAS/NRC 1979) and the urinary level is 0.5 mg/g creatinine (Elinder 1986). S everal studies have reported increased levels of zinc in the serum and urine of humans and animals after inhalation, oral, or dermal exposure to zinc (Agren et al. 1991; Bentley and Grubb 1991; Brandao-Neto et al. 1990a; Hallmans 1977; Hamdi 1969; Keen and Hurley 1977; Neve et al. 1991; Statter et al. 19818; Sturniolo et al. 1991). However, relationships between serum and/or urine levels and zinc exposure levels have not been established.

Hair and nail samples provide a lasting record of long-term metal intake possibly over weeks or months (Hayashi et al. 1993; Wilhelm et al. 1991). Mean zinc concentrations of 129-179 μg/g have been estimated for nails (Hayashi et al. 1993; Wilhelm et al. 1991) and 102-258 μg/g for hair (Folin et al. 1991; McBean et al. 1971; Provost et al. 1993; Wilhelm et al. 1991). Most investigators have found a poor correlation between hair and plasma zinc levels since the zinc in hair does not exchange with the body zinc pool (McBean et al. 1971; Rivlin 1983). Furthermore, measurements of zinc in hair can be affected by extraneous contamination of hair, contamination by sweat, location of hair sample (distance from scalp), hair coloring, and rate of hair growth (McBean et al. 1971; Rivlin 1983). Although the nail is considered more resistant to washing procedures than hair, external contamination and uncertainties regarding the length and period of exposure reflected by the observed zinc concentration limit this measurement as a biomarker of exposure for zinc (Wilhelm et al. 1991).

2.5.2 Biomarkers Used to Characterize Effects Caused by Zinc

The respiratory tract is the most sensitive target organ for zinc following inhalation exposure. Inhalation of zinc oxide results in a syndrome referred to as metal fume fever. Symptoms include fevers, chills, cough, listlessness, and metallic taste. Although oxides of several heavy metals

(antimony, aluminum, arsenic, cadmium, cobalt, copper, iron, lead, magnesium, manganese, mercury, nickel, selenium, silver, and tin) and pyrolysis products of fluorocarbon polymers (polytetrafluoroethylene [Teflon] and fluorinated polyethylene propylene) also produce metal fume fever (Ellenhorn and Barceloux 1988), this group of symptoms may be used as a nonspecific biomarker to identify inhalation exposure to zinc oxide.

The target organs associated with oral zinc exposure include the gastrointestinal tract, blood, immune system, and pancreas. The toxic effects observed after oral exposure to zinc include nausea, vomiting, diarrhea, decreased hemoglobin and hematocrit levels, immune suppression, increased serum amylase and lipase, and decreased HDL cholesterol levels. (A more detailed discussion of effects associated with exposure to zinc is presented in Section 2.2.) However, nausea, vomiting, and diarrhea may be observed following exposure to any gastrointestinal irritant. Increases in serum amylase and lipase are also markers for pancreatic damage; therefore, any condition resulting in pancreatitis (i.e., biliary tract disease [gallstones], alcoholism, trauma, inflammation, blood-borne bacterial infections, viral infections, ischemia, and drugs such as azathioprine, thiazides, sulfonamides, and oral contraceptives) would result in similar increases in these enzymes (Cotran et al. 1989). A hypochromic microcytic anemia that is not responsive to iron supplements may indicate exposure to zinc; however, such anemia may also retlect copper, pyridoxine, or cobalt deficiency, lead intoxication, poor diet, or chronic blood loss (Suber 19S9).

Thus, none of the above-mentioned effects observed after exposure to zinc is specific to zinc exposure. However, the combination of these toxic effects may be indicative of zinc overexposure. Additional information on the health effects of zinc may be found in Section 2.2.2. Additional information on biomarkers for renal, hepatobiliary, immune, and nervous system effects may be found in the CDC/ATSDR (1990) and OTA (1990) reports listed in Chapter 8.

Increased erythrocyte metallothionein may be an index of zinc exposure in humans (Grider et’al. 1990). Daily supplementation of 50 mg zinc/day to subjects for at least 7 days caused a seven-fold increase in metallothionein concentration in erythrocytes. At least 3-4 days were required before an increase in metallothionein is observed. This biomarker of exposure is only useful for recent zinc exposure because the metallothionein levels decreased approximately a week after discontinuation of a 63-week supplementation of zinc (Grider et al. 1990). Fourteen days after discontinuation of zinc supplements, metallothionein levels were reduced by 61%.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Zinc is an essential element obtained from the diet. Many different metals and nutrients interact with the absorption, distribution, and excretion of zinc. However, information was not found concerning interactions that increase the toxicity of zinc or other substances in the presence of zinc. Zinc administration may increase the toxicity of lead; however, the data are conflicting (Cerklewski and Forbes 1976; Hsu et al. 1975).

Metallothionein, a sulfhydryl-rich protein inducible by certain divalent cations and a variety of other agonists, is involved in the interaction between zinc and other metals such as copper (Wapnir and Balkman 1991). Inhibition of intestinal copper absorption by zinc may demonstrate competition between the two metals at the brush border of the lumen (Wapnir and Balkman 1991). Dietary intake of copper (1, 6, and 36 mg/kg) or zinc (5, 30, and 180 mg/kg) do not significantly alter the absorption of the other (Oestreicher and Cousins 1988), but when zinc levels are much higher than copper levels, copper absorption is depressed (Fischer et al. 1981). High levels of dietary zinc are known to induce de novo synthesis of metallothionein in the intestinal mucosal cell. Both copper and zinc appear to bind to the same metallothionein protein; however, copper has a higher affinity for metallothionein than zinc and displaces the zinc that is attached to the metallothionein (Ogiso et al. 1979). Copper complexed with metallothionein is retained in the mucosal cell, relatively unavailable for transfer to plasma, and is excreted in the feces when the mucosal cells are sloughed off (Fischer et al. 1981; L'Abbe and Fischer 1984b). A number of factors influence the effect of dietary zinc on copper metabolism, including the amount of copper and zinc in the diet, the zinc-to-copper ratio, age of the individual, and the duration of exposure to high zinc levels (Johnson and Flagg 1986).

Physiological interactions of zinc and cadmium have been discussed in a number of reviews (EPA 1980c; NAS 1980; Underwood 1977). Exposure to cadmium may cause changes in the distribution of zinc, with accumulation of zinc in the liver and kidney. This accumulation in the liver and kidney may result in a deficiency in other organs, particularly if the dietary intake of zinc is marginal. *In vitro* data demonstrate that zinc and cadmium enter renal proximal cells by a saturable, carrier-mediated process and a non-saturable pathway (Gachot and Poujeol 1992). At low cadmium doses, cadmium and zinc compete for a common transport carrier system in renal proximal cells. It is hypothesized that, at high doses, the subcellular microtubule system is

disrupted by cadmium, which may interfere with changes in carrier configuration that are necessary for transport of the metals (modification of the cytoskeleton), and thereby lead to noncompetitive inhibition between cadmium and zinc (Gachot and Poujeol 1992). Combined treatment with cadmium and zinc in primary cultures of kidney cells resulted in enhanced toxicity of cadmium (Yoshida et al. 1993); however, pretreatment with a nontoxic concentration of zinc caused increased induction of metallothionein synthesis and partial protection against cadmium (Yoshida et al. 1993).

Cadmium is 10 times more efficient than zinc in metallothionein induction *in vitro* (Harford and Sarkar 1991). Induction by either cadmium or zinc alone is saturable; however, simultaneous administration of cadmium and zinc results in induction of metallothionein in an additive manner. The additive effect on metallothionein induction may involve binding of the metals either to two or more metallothionein promoter binding proteins or separate sites on the same promoter binding protein (Harford and Sarkar 1991).

Zinc acetate pretreatment in the mouse TRL-1215 cell line reduced single-strand DNA damage associated with cadmium exposure (Coogan et al. 1992). Diminished cadmium-induced DNA damage was not due to decreased cadmium burden in the zinc-pretreated cells. Instead, cadmium levels were actually greater than those in non-pretreated cells (Coogan et al. 1992). Metallothionein levels were elevated in these cells, suggesting that zinc pretreatment affects cadmium genotoxicity by inducing metallothionein which may sequester cadmium from genetic material. In contrast, simultaneous exposure to cadmium and zinc decreased cadmium accumulation in the cells, perhaps because of direct competition for a common transport mechanism (Coogan et al. 1992).

Zinc acetate reduced or prevented cadmium carcinogenesis in the prostate, in the testes, or at the injection site in rats (Gunn et al. 1963a, 1964; Waalkes et al. 1989). The effect of zinc on the cadmium-induced carcinogenesis appeared to be dependent on dose, route, and target site. Sustained levels of zinc inhibited cadmium-induced injection sarcomas but had no effect on the incidence of testicular Leydig cell tumors (Waalkes et al. 1989).

Excessive dietary zinc has been shown to induce a reversible copper deficiency and anemia in experimental animals (Magee and Matrone 1960; Murthy and Petering 1976; O'Dell 1969;

Underwood 1977; Wapnir and Balkman 1991). Similar effects have been seen in humans receiving long-term treatment with zinc (Porter et al. 1977; Prasad et al. 1978). However, no significant decreases in plasma copper levels were observed in humans receiving zinc for 6 weeks or 6 months (Henkin et al. 1976; Samman and Roberts 1987) or in mice administered zinc for l-12 weeks (Sutomo et al. 1992). A reduction in erythrocyte superoxide dismutase (an index of metabolically available copper), without a decrease in plasma copper levels, was exhibited following exposure to high amounts of ingested zinc (Fischer et al. 1984). These findings suggest that superoxide dismutase may be a sensitive indicator of zinc-copper interaction.

Cobalt has been demonstrated to induce seminiferous tubule damage and degeneration (vacuole formation, sloughing of cells, giant cell formation) in the testes of mice following exposure for 13 weeks (Anderson et al. 1993). Coadministration of cobalt and zinc chloride in the drinking water resulted in complete or partial protection in 90% of the animals. The sites of competitive interaction between zinc an cobalt were not established in the study; however, the authors postulated that the mechanism(s) may be similar to those involved in prevention of cadmium toxicity by zinc.

The effect of tin on heme biosynthesis appears to be dependent on the concentration of zinc (Chmielnicka et al. 1992). Oral administration of tin can affect the heme synthesis by inhibiting δ-aminolevulinic acid dehydratase (ALAD) activity in blood, Zinc is required for ALAD activity and provides a protective role in heme synthesis by increasing the activity of ALAD. It is postulated that when the tin and zinc are coadministered, these metals are probably attaching to similar binding sites in the ALAD enzyme (Chmielnicka et al. 1992).

Calcium decreases the bioavailability of zinc; the converse is also true (Heth and Hoekstra 1965; Spencer et al. 1992). Oral zinc administration is associated with decreased calcium levels in the serum and in the bone of rats (Yamaguchi et al. 1983). Zinc inhibited calcium uptake in rat brush border membrane vesicles, possibly by competing directly at high-affinity calcium binding sites (Roth-Bassell and Clydesdale 1991). The interaction of calcium and zinc is apparently dose related; intestinal absorption of calcium at a low calcium intake (230 mg/day) was inhibited at a high zinc intake of 140 mg/day but not at a lower zinc intake of 100 mg/day (Spencer et al. 1992).

Pretreatment with zinc has been shown to reduce hepatotoxicity induced by xenobiotics such as acetaminophen, bromobenzene, carbon tetrachloride, D-galactosamine, gentamicin, and salicylate (Cagen and Klaassen 1979; Gunther et al. 1991; Hu et al. 1992; Szymanska et al. 1991; Yang et al. 1991). The protective effect of zinc against carbon tetrachloride toxicity is dose dependent at high dose levels of zinc, probably because of sequestering of toxic metabolites of carbon tetrachloride by metallothionein (Cagen and Klaassen 1979). Similarly, the protective action of zinc against bromobenzene and acetaminophen appears to be associated with elevated metallothionein levels (Szymanska et al. 1991). Inhibition of lipid peroxidation may be the basis for the protective effect of zinc against hepatic damage induced by D-galactosamine in rats (Hu et al. 1992). Zinc may be elevating NADPH (nicotinamide adenine dinucleotide phosphate) content in the cell, resulting in regeneration of glutathione, which increases the antioxidative ability of hepatic cells. Salicylate-induced hepatic alterations (increased lipid droplets and iron, reduced glycogen) (Gunther et al. 1991) and gentamicin-induced proximal tubular necrosis (Yang et al. 1991) were diminished in rats pretreated with injections of zinc chloride and zinc sulfate, respectively. This finding corresponded to a dramatic increase in metallothionein content with combined treatment of salicylate and zinc compared to a less significant increase with salicylate alone.

Animal studies suggest that the administration of zinc may also inhibit tumor growth. Forty weeks after exposure, the incidence of injection site sarcomas was 40-60% in rats receiving simultaneous intramuscular administration of nickel subsulfide and zinc oxide compared to an incidence of 100% following administration of nickel subsulfide alone (Kasprzak et al. 1988). Supplementing drinking water with zinc sulfate reduced the incidence of 9,10-dimethyl-1,2-benzanthraceneinduced tumors in the cheek pouches of mice (Poswillo and Cohen 1971). Zinc decreased DNA synthesis in hepatomas induced by 3’-methyl-4-dimethylaminoazobenzene (Duncan and Dreosti 1975). The investigators speculated that the changes were due to inhibited cell division cycle at the level of DNA replication.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to zinc than will most persons exposed to the same level of zinc in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase

susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects on clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

No specific data regarding human subpopulations that are unusually susceptible to the toxic effects of zinc were located. Healthy elderly people have been shown to have greater daily zinc intake than housebound elderly people (Bunker et al. 1987; Prasad 1988). Data from animal studies indicate that certain human subpopulations may be more susceptible to excess zinc because of zinc's depleting effect on copper (Underwood 1977). People who are malnourished or have a marginal copper status may be more susceptible to the effects of excessive zinc than people who are adequately nourished (Underwood 1977).

Hepatic zinc levels are elevated in patients with hemochromatosis, a genetic disease associated with increased iron absorption from the intestine (Adams et al. 1991). The chronic iron loading that occurs could result in hepatic metallothionein induction leading to the accumulation of zinc because metallothionein has a greater affinity for zinc than iron. These individuals may, therefore, have a greater likelihood of developing toxicity with zinc exposure levels that do not normally result in any symptoms in the general population.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to zinc. However, because some of the treatment discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to zinc. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

General recommendations for the management and treatment of patients following acute exposure to zinc include removal of the victim from the contaminated area and removal and isolation of contaminated clothing, jewelry, and shoes (Bronstein and Currance 19818; Stutz and Janusz 1988). Excess contaminant is gently brushed away and excess liquids blotted with absorbent material. Measures that are appropriate to the route of exposure are taken to remove zinc from the body. Exposed eyes are flushed immediately with water, followed as soon as possible with irrigation of each eye with normal saline. Exposed skin is washed immediately with soapy water. Administration of ipecac to induce emesis, gastric lavage, ingestion of activated charcoal, and cathartics have been recommended to decrease the gastrointestinal absorption of zinc (Burkhart et al. 1990; Ellenhorn and Barceloux 19%). Because zinc causes nausea and vomiting following exposure by the oral route, use of emetic agents may be unnecessary. Ipecac administration may be contraindicated following ingestion of caustic zinc compounds such as zinc chloride. The large amounts of phosphorus and calcium in milk and cheese, and phytate in brown bread, may reduce absorption of zinc from the gastrointestinal tract (Pecoud et al. 1975). Therefore, if vomiting and diarrhea are not prohibitive, ingestion of dairy products or brown bread may also reduce gastrointestinal absorption of zinc. In a study of intestinal absorption of zinc in iron-deficient mice, the uptake of zinc from the gut was inhibited by adding iron to the duodenal loop system. The proposed mechanism was that iron and zinc shared a common gut mucosal binding site (Hamilton et al. 1978). However, it is unknown whether ingestion of iron supplements would be effective in reducing absorption of zinc overdoses.

2.8.2 Reducing Body Burden

Zinc is an essential trace element that is normally found in tissues and fluids throughout the body and is under homeostatic control (NAS/NRC 1989b). Increased levels have been observed in the heart, spleen, kidneys, liver, bone, and blood of animals following subchronic oral exposure to zinc (Llobet et al. 1988a) indicating that some zinc accumulation occurs during excess intakes. The greatest increases were observed in bone and blood.

Administration of the chelating agent, calcium disodium ethylene diaminetetraacetate ($CaNa_2EDTA$), is the treatment of choice for reducing the body burden of zinc in humans

following exposure to high levels (Ellenhorn and Barceloux 19%). Ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), and dimercaprol (BAL) are the most common antidotes used in the treatment of human zinc intoxications (Murphy 1970; Spencer and Rosoff 1966). Markedly elevated serum zinc levels in a young child who ingested a zinc chloride solution were normalized by intravenously administering a single small dose of $CaNa_2EDTA$ (11.5 mg/kg) (Potter 1981). Use of chelation therapy (administration of BAL) was reported in a case study of a 16-year-old boy who ingested 12 g of metallic zinc (Murphy 1970). The boy exhibited lethargy and elevated blood zinc levels that were both reversed following intramuscular administration of BAL. Chelation therapy has been demonstrated to increase the urinary excretion of zinc 22-fold (Spencer and Rosoff 1966). Intravenous and nebulized N-acetylcysteine (another metal chelating agent) have also been observed to increase urinary zinc excretion and decrease plasma levels following inhalation of zinc chloride smoke (Hjortso et al. 1988).

The efficacy of 16 different chelating agents as possible antidotes for acute oral zinc exposure has been determined in mice (Llobet et al. 1988b). The most efficient chelators were DTPA, cyclohexanediamine-tetraacetic acid (CDTA), and EDTA. Increased urinary levels of zinc and decreased bone and liver zinc levels were observed following administration of the chelators. The maximum efficiency of the chelators was observed when they were administered 0-.167-12 hours after zinc exposure (Domingo et al. 1988a, 1988b).

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Anemia has been observed in humans and animals after oral exposure to zinc. It has been postulated that excess zinc intake may result in copper deficiency (mechanisms of action are discussed in Section 23.5). The anemia observed following zinc intake is believed to be caused by the copper deficiency. Administration of copper has been shown to be effective in increasing the hemoglobin levels (Porter et al. 1977; Smith and Larson 1946).

The exact mechanism of metal fume fever (a syndrome consisting of a leukocytosis with chills, fever, cough, myalgias, headache, weakness, and dyspnea) is unknown (Ellenhorn and Barceloux 1988), but respiratory tract inflammation and the development of an immune complex reaction have been proposed (McCord 1960).

In severe cases, inhalation of zinc chloride has resulted in advanced pulmonary fibrosis and fatal respiratory distress syndrome (Evans 1945; Hjortso et al. 1988; Milliken et al. 1963). L-3,4-Dehydroproline was given to two soldiers after inhaling a high concentration of zinc chloride smoke (also contained other chemicals) in an attempt to inhibit collagen deposition in the lungs (Hjortso et al. 1988). This therapy did not prevent respiratory failure.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of zinc is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of zinc.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Zinc

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to zinc are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of zinc. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as “data needs.” A data need, as defined in ATSDR’s Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989) is

ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

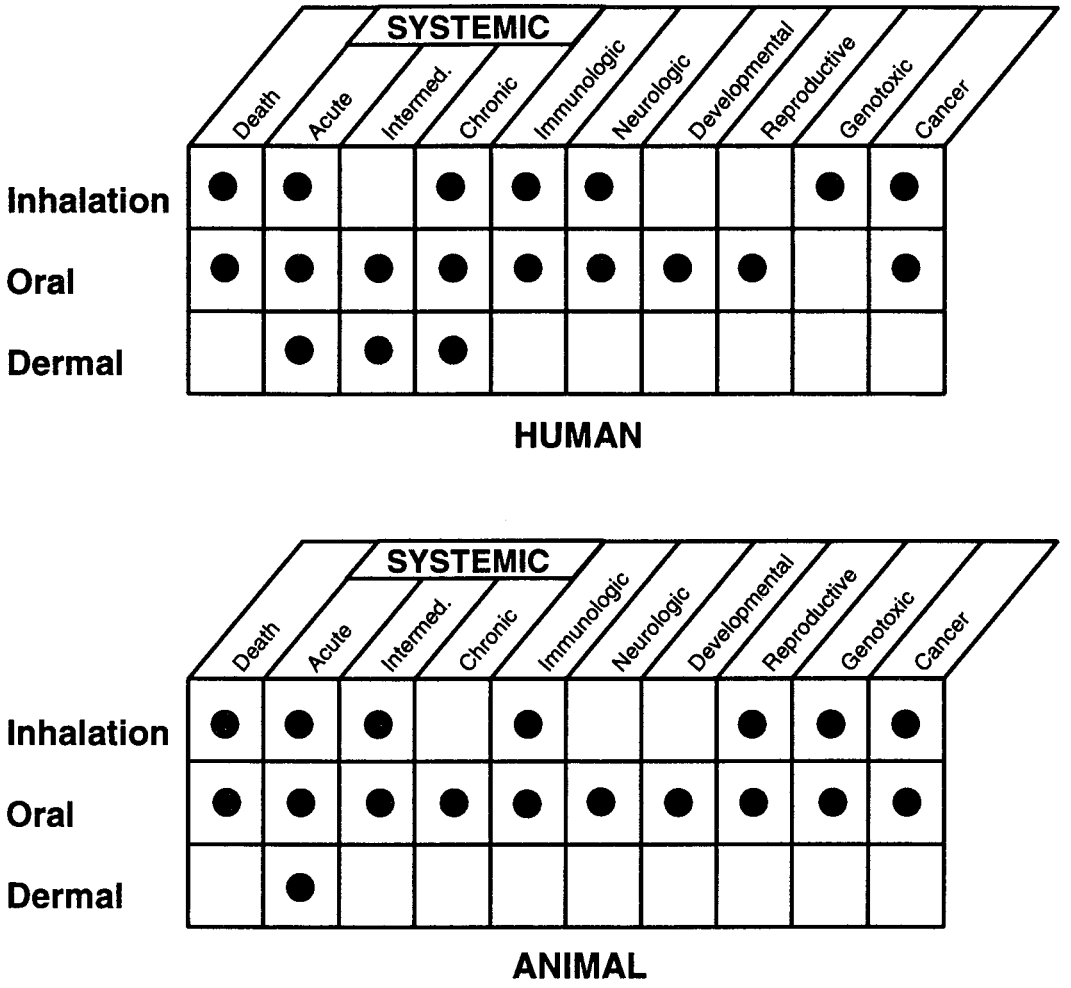
Figure 2-3 indicates whether a particular health effect end point has been studied for a specific route and duration of exposure. There is little information concerning death in humans after inhalation, oral, or dermal exposure to zinc. Several case studies report death after exposure to extremely high levels of zinc chloride and other components of zinc chloride smoke (Evans 1945; Hjortso et al. 1988; Milliken et al. 1963).

Systemic effects of acute inhalation exposure to generally unspecified levels of various zinc compounds in humans have been reported in several clinical case studies (Blanc et al. 1991; Brown 1988; Hjortso et al. 1988; Matarese and Matthews 1966; Vogelmeier et al. 1987). Case studies and experimental studies of systemic effects in humans following acute, intermediate, and chronic oral exposures are available (Anonymous 1983; Black et al. 1988; Brandao-Neto et al. 1990a; Chandra 1984; Chobanian 1981; Hale et al. 1988; Hallbook and Lanner 1972; Hoffman et al. 1988; Hooper et al. 1980; Malo et al. 1990; Moore 1978; Patterson et al. 1985; Porter et al. 1977; Potter 1981; Prasad et al. 1978). Experimental studies in humans following acute, intermediate, and chronic dermal exposures were located for hematological, dermal, and ocular effects (Agren 1990; Evans 1945; Fischer et al. 1984; Turner 1921; Yadrick et al. 1989).

Information concerning respiratory effects of acute inhalation exposure to zinc in animals is available (Amdur et al. 1982; Drinker and Drinker 1928; Lam et al. 1982, 1988). One study (Marrs et al. 1988) was located regarding other systemic effects in animals following inhalation exposure to zinc for an intermediate exposure duration. Information regarding systemic effects of zinc following oral exposure in animals is available for acute, intermediate, and chronic exposure durations (Allen et al. 1983; Anderson and Danylchuk 1979; Aughey et al. 1977; Bentley and Grubb 1991; Domingo et al. 1988a; Drinker et al. 1927; Jenkins and Hidiroglou 1991; Katya-Katya et al. 1984; Klevay and Hyg 1973; Llobet et al. 198Sa; Maita et al. 1981; Straube et al. 1980; Walters and Roe 1965). One acute dermal study evaluated dermal irritancy in animals (Lansdown 1991).

Immunological effects were reported in humans following inhalation exposure to zinc oxide (Blanc et al. 1991; Farrell 1987). Another study reported potential adverse immunological effects

FIGURE 2-3. Existing Information on Health Effects of Zinc



following oral exposure of humans (Chandra 1984). Clinical symptoms suggestive of neurological effects have been reported by humans following inhalation exposure (Rohrs 1957; Sturgis et al. 1927; Wilde 1975) or oral exposure (Anonymous 1983; Murphy 1970; Potter 1981) to zinc. There were studies that examined reproductive and developmental effects in women orally exposed to zinc during their pregnancies (Kynast and Saling 1986; Mahomed et al. 1989; Simmer et al. 1991).

One study examined immunological and reproductive effects in animals following inhalation exposure to zinc chloride (Marrs et al. 1988). Immunological and neurological end points were evaluated in animals following oral exposure to zinc (Bleavins et al. 1983; Kozik et al. 1980, 1981; Schiffer et al. 1991). Information regarding developmental and reproductive effects in animals after oral exposure to zinc is available (Cox et al. 1969; Ketcheson et al. 1969; Kinnamon 1963; Mulhern et al. 1986; Pal and Pal 1987; Schlicker and Cox 1968; Sutton and Nelson 1937). Studies regarding genotoxicity in animals after inhalation and oral exposures to zinc are limited (Gupta et al. 1991; Kowalska-Wochna et al. 1988; Voroshilin et al. 1978).

Epidemiological studies regarding carcinogenicity after inhalation and oral exposure to zinc are available (Logue et al. 1982; Neuberger and Hollowell 1982; Philipp et al. 1982; Stocks and Davies 1964); however, they were not well controlled and the data are of little significance. Studies are available regarding carcinogenicity in animals after inhalation and oral exposure to zinc (Marrs et al. 1988; Walters and Roe 1965). However, the studies have several deficiencies that limit their usefulness.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. Symptoms of metal fume fever (headache, fever, leukocytosis, myalgias) have been observed in humans acutely exposed to airborne zinc oxide (Blanc et al. 1991; Brown 1988; Drinker et al. 1927b; Sturgis et al. 1927). Acute oral exposure to zinc has resulted in gastrointestinal disturbances (abdominal pain, nausea, vomiting, esophageal erosion), evidence of pancreatic damage (increased serum amylase and lipase levels), and decreased levels of serum cortisol in humans (Anonymous 1983; Brandao-Neto et al. 1990a; Chobanian 1981; Murphy 1970; Potter 1981). Acute dermal exposure to zinc oxide has not been shown to be irritating to human skin (Agren 1990). Toxic effects similar to those observed for metal fume fever have been observed in guinea pigs (Amdur et al. 1982; Lam et al. 1985). In addition to

LD_{50} data, only one reliable study assessed the acute oral toxicity of zinc compounds in animals. Pancreatic, gastrointestinal, and liver damage were observed in sheep (Allen et al. 1983). It is doubtful that sheep (ruminant animals) are an appropriate model for toxicity of orally administered zinc in humans. The dermal toxicity of several zinc compounds has been tested in rabbits, guinea pigs, and mice (Lansdown 1991). Zinc acetate, zinc chloride, and zinc sulfate have irritating properties. Skin irritation was not observed in rabbits, guinea pigs, or mice after zinc oxide paste application (Lansdown 1991).

The animal data (Amdur et al. 1982; Drinker and Drinker 1928; Lam et al. 1982, 1988) corroborate occupational exposure studies that indicate metal fume fever is an end point of concern. However, other possible targets of toxicity have not been examined. Thus, an acute inhalation MRL cannot be derived. A large amount of the human oral exposure data is in the form of case reports, and a great deal of uncertainty exists regarding the dose levels. The uncertainty about whether sheep are a good model for humans precludes using these data to derive an oral MRL for acute-duration exposure. Additional studies involving acute exposure to zinc compounds by all routes of exposure would be helpful to identify target organ and doseresponse relationships. There are groups who may be exposed to zinc at hazardous waste sites for brief periods; therefore, this information is important.

Intermediate-Duration Exposure. Metal fume fever was observed in an individual exposed to zinc fumes and zinc powder for approximately 1 month (Malo et al. 1990). Anemia and decreased levels of HDL cholesterol have been observed in humans taking high doses of zinc supplements (Chandra 1984; Hoffman et al. 1988; Hooper et al. 1980). Intermediate-duration dermal exposure to zinc oxide dust has resulted in pustuIar lesions, but these lesions were attributed to clogging of the sebaceous glands resulting from poor hygiene (Turner 1921). Rats, mice, and guinea pigs exposed to smoke containing zinc chloride and other compounds had evidence of lung irritation (Marrs et al. 1988). No intermediate-duration animal dermal studies were located. In animals that ingested zinc for an intermediate duration, anemia and kidney and pancreas damage were observed (Bentley and Grubb 1991; Drinker et al. 1927d; Jenkins and Hidiroglou 1991; Llobet et al. 1988a; Maita et al. 1981; Straube et al. 1980).

Only one case report regarding human intermediate-duration inhalation exposure was located, and this study did not report the exposure level (Malo et al. 1990). Thus, an intermediate-duration

inhalation MRL could not be derived. The less serious LOAELs (decreased serum HDL cholesterol) identified in the Hooper et al. (1980) and Chandra (1984) human oral exposure studies could be used as the basis of an intermediate-duration oral MRL; however, evidence regarding this effect is inconsistent (Bogden et al. 1988; Hale et al. 1988; Samman and Roberts 1988). In addition, the resulting MRL would be ≈l0-fold lower than the RDA of 15 mg/day (0.21 mg zinc/kg/day). An intermediate-duration oral MRL was derived for zinc based on hematological effects (decreased hematocrit, serum ferritin, and erythrocyte superoxide dismutase) in women given zinc gluconate supplements for 10 weeks (Yadrick et al. 1989). The toxic effects of intermediate-duration exposure to zinc compounds are relatively well characterized for the oral route. There are insufficient toxicokinetic data to determine if the toxic effects observed following oral exposure would occur following inhalation or dermal exposure. Inhalation and dermal studies would be useful to determine possible target organs and dose-response relationships. There are populations surrounding hazardous waste sites that might be exposed to zinc compounds for similar durations.

Chronic-Duration Exposure and Cancer. No exposure-related effects on lung function were observed in a group of welders chronically exposed to zinc (Marquart et al. 1989). Anemia has been observed in humans following ingestion of high doses of zinc supplements (Broun et al. 1990; Hale et al. 1988; Porter et al. 1977; Prasad et al. 1978). Chronic-duration dermal exposure to zinc oxide dust has resulted in pustular lesions, but these were attributed to clogging of the sebaceous glands resulting from poor hygiene (Batchelor et al. 1926). No chronic-duration inhalation or dermal studies in animals were located. Pancreatic damage was observed in mice after chronic exposure to zinc sulfate in drinking water (Aughey et al. 1977).

A chronic-duration inhalation MRL could not be derived for zinc because neither of the inhalation studies reported the levels of airborne zinc. Due to a lack of adequate chronicduration oral studies, the intermediate-duration oral MRL was adopted as the chronic-duration oral MRL, based on hematological effects (decreased hematocrit, serum ferritin, and erythrocyte dismutase) in women given zinc gluconate supplements for 10 weeks (Yadrick et al. 1989). Additional studies involving chronic exposure to zinc compounds by all routes of exposure would be helpful to identify dose-response relationships.

Although there are several human and animal carcinogenicity studies, the limitations of these studies preclude their use in assessing the carcinogenicity of zinc (Logue et al. 1982; Neuberger and Hollowell 1982; Walters and Roe 1965). Carcinogenicity studies by all routes of exposure would be useful.

Genotoxicity. Several *in vitro* microbial gene mutation assays were negative (Marzin and Vo Phi 1985; Nishioka 1975; Thompson et al. 1989; Venitt and Levy 1974; Wong 19&S), but evidence from gene mutation assays in mammalian cells is mixed (Amacher and Paillet 1980; Thompson et al. 1989). An increase in the occurrence of chromosomal aberrations was observed *in vitro* in human lymphocytes (Deknudt and Deminatti 1978) and *in vivo* in rats and mice (Deknudt and Gerber 1979; Gupta et al. 1991; Kowalska-Wochna et al. 1988; Voroshilin et al. 1978). Increased sister chromatid exchange was observed *in vivo* in rat bone marrow (Kowalska-Wochna et al. 1988). However, while there are sufficient *in vivo* data establishing the clastogenicity of zinc, data regarding the mutagenicity of zinc are conflicting. Studies designed to assay different types of genotoxicity (i.e., mutagenicity in mammalian cells, effect of excess zinc on DNA replication) would be useful for determ.ining the genotoxic potential of zinc.

Reproductive Toxicity. No complications occurred in the pregnancies of women exposed to daily doses of zinc sulfide during the last two trimesters (Mahomed et al. 1989). No studies were located regarding the reproductive toxicity of zinc in humans after inhalation or dermal exposure. Increased pre-implantation loss and reproductive dysfunction in rats were observed in oral exposure studies (Pal and Pal 1987; Sutton and Nelson 1937). No histological changes in reproductive organs were observed in rats, mice, or guinea pigs following inhalation exposure to zinc chloride smoke, but reproductive function was not assessed (Marrs et al. I988). No dermal reproductive toxicity studies in animals were located. Inhalation and dermal studies assessing reproductive function would be useful to determine whether zinc has the potential to cause reproductive effects by these routes. An oral reproductive toxicity study in a different animal strain as well as a multigeneration study, including reproductive organ pathology, would be useful

Developmental Toxicity. No studies were located regarding the potential of zinc to cause developmental effects in humans after inhalation or dermal exposure. In a very brief report of a human study in which pregnant women received high-doses of zinc supplements during the last

trimester of pregnancy, an increased incidence of stillbirths and one premature delivery were observed (Kumar 1976). This study, however, has many limitations. Increased fetal resorptions were observed in rats after oral exposure to zinc (Schlicker and Cox 1968). No studies were located regarding developmental toxicity in animals after inhalation or dermal exposure to zinc. Additional inhalation, oral, and dermal exposure studies in animals would be useful to predict whether developmental effects should be a concern for humans exposed to zinc.

Immunotoxicity. Metal fume fever is believed to be an immune response to zinc oxide. A correlation between the concentration of airborne zinc and the number of all types of T cells (helper, inducer, suppressor, and killer) in the bronchoalveolar lavage fluid of humans, possibly related to the onset of metal fume fever, was observed in an acute-duration inhalation study (Blanc et al. 1991). Impaired immune response in humans has been reported in an intermediate-duration oral study (Chandra 1984). No immune effects were observed in mice after oral exposure to zinc (Schiffer et al. 1991). There is some limited information to suggest that the immune system is a target of zinc toxicity. A battery of immune function tests after inhalation, oral, and dermal exposure to zinc compounds would be useful in determining if zinc is immunotoxic.

Neurotoxicity. Staggering gait and hallucinations were reported in an individual who intentionally inhaled metallic paint aerosols (Wilde 1975). Because there was simultaneous exposure to copper and hydrocarbons, this study cannot be used to assess the neurotoxic potential of zinc. Nonspecific signs and symptoms of neurotoxicity (light-headedness, dizziness, headache, lethargy) have been reported by humans following acute oral exposure to zinc (Murphy 1970; Potter 1981). Very limited data suggest that high oral doses of zinc can cause minor neuron degeneration and alteration of secretion of the hypothalamus in rats (Kozik et al. 1980, 1981). No studies were located regarding neurotoxic effects in animals after inhalation or dermal exposure to zinc. Additional studies by all routes of exposure would be useful to determine if exposure to zinc compounds would result in neurotoxicity.

Epidemiological and Human Dosimetry Studies. Acute high-level exposure to zinc by inhalation resulted in respiratory irritation and metal fume fever (Blanc et al. 1991; Hjortso et al. 1988; Johnson and Stonehill 1961; Linn et al. 1981; Schenker et al. 1981; Sturgis et al. 1927). Welders are a subpopulation of workers who have a high potential for exposure to zinc oxide.

Most of the available studies did not report exposure levels or used a small number of subjects. Studies that correlate occupational exposure to zinc with health effects would be useful. A number of human oral exposure studies have shown that excess levels of zinc can result in anemia, pancreatic damage, decreased serum HDL cholesterol levels, and immunotoxicity (Black et al. 1988; Chandra 1984; Hooper et al. 1980). There are insufficient data for establishing dose-response relationships. Studies designed to establish dose-response relationships would be useful for establishing cause/effect relationships and future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect

Exposure. Increased serum and urine levels of zinc were observed in humans and animals after inhalation, oral, or dermal exposure to zinc (Bentley and Grubb 1991; Brandao-Neto et al. 1990b; Hallmans 1977; Keen and Hurley 1977). However, the relationships between zinc exposure levels and the levels of zinc in biological fluids have not been established. Hair and nail samples may be a potential biomarker for long-term zinc exposure (McBean et al. 1971; Rivlin 1983; Wilhelm et al. 1991); however, no correlation has been demonstrated between these parameters and zinc exposure levels. Development of a biomarker with more exposure and dose data would aid in future medical surveillance that could lead to better detection of zinc exposure.

Effect. Several potential biomarkers for the effects of zinc have been identified. These include increased levels of serum amylases and lipase, indicative of pancreatic damage; non-iron responsive anemia; and decreased HDL cholesterol levels (Suber 1989). However, these biomarkers of effect are not specific for zinc. These biomarkers cannot be used for dosimetry. A potential biomarker of exposure for recent exposures to zinc is increased erythrocyte metallothionein concentrations (Grider et al. 1990). Further investigation of serum biomarkers of effect, particularly for chronic exposure, in zinc-exposed populations would be useful to determine whether exposed populations may be experiencing adverse health effects as the result of zinc exposures.

Absorption, Distribution, Metabolism, and Excretion. Absorption of zinc in humans after oral exposure to high levels has been well described (Aamodt et al. 1983; Hunt et al. 1991; Reinhold et al. 1991; Sandstrom and Abrahamson 1989; Sandstrom and Cederblad 1980; Sandstrom and

Sandberg 1992; Spencer et al. 1985). However, quantitative evidence of zinc absorption in humans after inhalation or dermal exposure is very limited. It is known that workers exposed to zinc oxide fumes who experience toxic effects have elevated levels of zinc in plasma and urine (Hamdi 1969). However, it remains to be established whether the elevated levels are the result of the pulmonary absorption or of the swallowing of particles leading to gastrointestinal absorption. Toxic effects have also been observed in humans after dermal exposure (DuBray 1937) indicating dermal absorption.

Information regarding the absorption of zinc in animals following inhalation exposure was limited to lung retention data (Gordon et al. 1992; Hirano et al. 1989). However, there was information to assess the extent of absorption following oral exposure (Davies 1980; Galvez-Morros et al. 1992; Johnson et al. 1988; Weigand and Kirchgessner 1992). Evidence is limited regarding dermal absorption in animals, but it indicates that zinc sulfate and zinc oxide can penetrate the skin (Agren 1990; Agren et al. 1991; Gordon et al. 1981; Hallmans 1977). Mechanistic data on the oral absorption is reported by Hempe and Cousins (1992); however, there is a lack of information regarding the mechanism of action of inhalation and dermal exposures.

Information on physiological levels and zinc distribution following subtoxic short-term exposures to zinc in humans and animals is abundant (NAS/NRC 1979; Wastney et al. 1986). Blood levels of zinc have been determined in humans following oral exposure to zinc sulfate (Neve et al. 1991; Statter et al. 1988; Sturniolo et al. 1991). Increased zinc tissue content has been seen after shortterm oral exposure in humans (Cooke et al. 1990; He et al. 1991; Llobet et al. 198Sa; Schiffer et al. 1991; Weigand and Kirchgessner 1992). Studies on tissue distribution in humans following high exposure to zinc for inhalation, oral, and dermal would be useful. There were no studies regarding blood or tissue distribution after acute, high-level exposures to zinc in animals following inhalation or dermal exposure. Additional mechanistic data on the transfer of zinc from respiratory and dermal absorption sites to the blood would be useful.

The principal excretion route of ingested zinc is through the intestines (Davies and Nightingale 1975; Reinhold et al. 1991; Wastney et al. 1986). There is a lack of information regarding the excretion of zinc in both animals and humans following inhalation and dermal exposure.

Therefore, additional studies designed to assess the toxicokinetic properties of zinc following inhalation and dermal exposures would be useful.

Comparative Toxicokinetics. Data suggest that humans and animals have similar target organs of zinc toxicity (Allen et al. 1983; Aughey et al. 1977; Black et al. 1988; Blanc et al. 1991; Brown 1988; Chandra 1984; Chobanian 1981; Drinker et al. 1927b, 1927d; Hoffman et al. 1988; Hooper et al. 1980; Katya-Katya et al. 1984; Kievay and Hyg 1973; Lam et al. 1982, 1985, 1988; Maita et al. 1981; Moore 1978; Murphy 1970; Smith and Larson 1946; Straube et al. 1980; Sturgis et al. 1927). Toxicokinetic studies have been performed in both humans and animals following oral exposure; however, data are limited for inhalation and dermal exposures. The animal model used most often to evaluate the toxicokinetics of zinc are rats (Agren et al. 1991; Alexander et al. 1981; Galvez-Morros et al. 1992; Hirano et al. 1989; Llobet et al. 1988a; Weigand and Kirchgessner 1992) and may be a good model for assessing the kinetics of zinc in humans.

Methods for Reducing Toxic Effects. No established methods or treatments for reducing the absorption of zinc were located. Studies that examined the effectiveness of emetics and cathartics in the prevention of zinc absorption would be useful. Once absorbed from the gastrointestinal tract, zinc bound to plasma albumin is distributed to the rest of the body. Zinc has a high affinity for proteins, and a number of chelating agents are effective in increasing urinary excretion of zinc following acute- and intermediate-duration administrations (Domingo et al. 1988a, 1988b; Llobet et al. 1989). Studies designed to examine the effectiveness of chelating agents following chronic zinc exposure would be useful in determining treatments to reduce the zinc body burden. Very little information is known about the absorption and distribution of zinc following inhalation or dermal exposure. Studies to determine the mechanisms of absorption and distribution would be useful for developing treatments or methods for reducing the toxic effects of zinc after inhalation or dermal exposure.

Although the exact mechanisms of many of the toxic actions of zinc are not known, the pathogenesis of metal fume fever following inhalation exposure (McCord 1960; Mueller and Seger 1985) and anemia following oral exposure (Prasad et al. 1978) are known. Studies to more clearly elucidate the mechanisms involved in metal fume fever and anemia and to determine the mechanisms involved in pancreatic damage and decreased HDL cholesterol levels would be useful. Therapy for metal fume fever is mainly supportive (Mueller and Seger 1985). Administration of

copper has been shown to be effective in alleviating zinc-induced anemia (Porter et al. 1977). Research into methods useful for mitigating metal fume fever and other adverse effects of zinc would be helpful.

2.9.3 On-going Studies

Currently, D.W. Christianson (University of Pennsylvania, Philadelphia, Pennsylvania) and C.A. Fierke (Duke University, Durham, North Carolina) are looking at redesigning the zinc binding site of the human carbonic anhydrase II enzyme and E. Kimura's group (Hiroshima University, Hiroshima, Japan) is examining the roles of zinc(I1) ion in zinc enzymes.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical identities of zinc and selected zinc compounds are provided in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of zinc and selected zinc compounds are listed in Table 3-2.

TABLE 3-1. Chemical Identity of Zinc and Selected Compounds[a]

Characteristic	Zinc	Zinc chloride	Zinc sulfate
Synonym(s)	Zinc dust; zinc powder	Butter of zinc; chlorure de zinc (French); zinc (chlorure de) (French); zinc butter; zinc chloride ($ZnCl_2$); zinc dichloride; zinco (cloruro di) (Italian); zinkchlorid (German); zinkchloride (Dutch)	Sulfate de zinc (French); sulfuric acid zinc salt; sulfuric acid, zinc salt (1:1); white copperas; white vitriol; zinc sulfate; zinc vitriol; zinci sulfas; zincum sulfuricum
Registered trade name(s)	Asarco; L 15; Blue powder; CI 77945; CI pigment Metal 6; Emanay zinc dust; Granular zinc; JASAD; Merrillite; PASCO	Tinning flux (DOT)[c]; AI3-04470; Zintrace	Bonazen[c]; Medizinc; Bufopto Zinc sulfate; Op-thal-zin; Optraex; Solvenzink; Verazinc; Zincate; Zincomed; Zinkosite; AI3-03967; Orazinc; Zinc-200; Zinklet; Neozin; Optised; Prefrin-Z; Visine-AC; Zincfrin; Zink-Gro
Chemical formula	Zn	$ZnCl_2$[d]	$ZnSO_4$[d]
Chemical structure	Zn	Cl-Zn-Cl	
Identification numbers:			
CAS registry	7440-66-6	7646-85-7	7733-02-0
NIOSH RTECS	ZG8600000	ZH1400000	ZH5260000
EPA hazardous waste	No data	No data	No data
OHM/TADS	7216955	7216957	7216958
DOT/UN/NA/IMCO	Zinc, powder or dust, UN 1436; zinc, powder or dust, zinc ashes, IMO 4.3; zinc ashes, UN 1435	Zinc chloride, anhydrous, UN 2331; zinc chloride, solution, UN 1840; zinc chloride, anhydrous, solution, IMO 8.3	NA 9161
HSDB	1344	1050	1063
NCI	No data	No data	No data

[a]All information obtained from HSDB 1993 except where noted
[b]All information with the exception of HSDB number obtained from NIOSH 1990
[c]HSDB 1990
[d]Merck 1983

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances; Zn = zinc

TABLE 3-1. Chemical Identity of Zinc and Selected Compounds[a] *(continued)*

Characteristic	Zinc sulfide	Zinc oxide[b]
Synonym(s)	Wurtzite (alpha)[c]; Sphalerite (beta)[c]; zinc monosulfide	Calamine[c]; Zincite[c]; cynku tlenek (Polish); zinc monoxide; C-Weiss 8 (German); Blanc de Zinc; zincum oxydatum; zinci oxydum; zinci oxicum
Registered trade name(s)	Albalith; Irtran Z; CI pigment white 7; Sachtolith; Zinc blende	Akro-Zinc Bar 85[c]; Actox 14; Actox 16; Actox 216; Amalox; Azodox; Azo 22; Cadox XX 78; Chinese white; CI 77947; CI pigment white 4; Emanay zinc oxide; Emar; Felling zinc oxide; Flores de zinci; Flowers of zinc; Green seal-8; Hubbuck's white; Kadox 15; Kadox 72; Kadox-25; ozide; Ozlo; Permanent white; Philosopher's wool Powder base 900; Protox types 166, 167, 168, 169, 267, 268; Red seal-9; Snow white; Vandem VAC; Vandem VOC; Vandem VPC; White seal-7; XX 203; XX 78; Zinc white; Zinca 20; Zincoid; Zn 0701T; Electrox 2500; GIAP 10; Outmine; Unichem ZO; XX 601
Chemical formula	ZnS	ZnO
Chemical structure	Zn=S	Zn=0
Identification numbers:		
CAS registry	1314-98-3	1314-13-2
NIOSH RTECS	No data	ZH4810000
EPA hazardous waste	D003	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	5802	5024
NCI	No data	No data

TABLE 3-2. Physical and Chemical Properties of Zinc and Selected Compounds[a]

Property	Zinc	Zinc chloride	Zinc sulfate
Molecular weight	65.38	136.29	161.44
Color	Bluish-white, lustrous metal; distorted hexagonal closepacked structure	White granules (very deliquescent) or fused pieces/rods; fume is white[c]	Colorless rhombic crystals[b]
Physical state	Solid	Solid	Solid
Melting point	419.5℃	290℃	600℃ (decomposes)
Boiling point	908℃	732℃	No data
Density (g/cm^3)	7.14 at 25℃	2.907 at 25℃	3.54 at 25℃[b]
Odor	No data	Odorless; fume has acrid odor[c]	Not determined[d]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water (mg/L)	Insoluble[b]	4.32×10^6 at 25℃; 6.14×10^6 at 100℃	Soluble in cold and hot water[b]; 1.7×10^6
Other solvent(s)	Soluble in acetic acid and alkali	1 g/1.3 mL alcohol; 1 g/2 mL glycerol; 1 g/0.25 mL 2% hydrochloroacetic acid	Slightly soluble in alcohol; soluble in methanol and glycerol[b]; 1 g/2.5 mL glycerol
Partition coefficients:			
K_d (mL/g)	0.1–8,000[e]; 40 (AVG)[f]; 939 in sandy loam soil; 12.2 in sandy soil[g]	No data	No data
Kow	No data	No data	No data
Koc	No data	No data	No data
Vapor pressure	1 mmHg at 487℃	1 mmHg at 428℃	Not determined
Henry's law constant	Not applicable	Not applicable	Not applicable
Autoignition temperature (Centigrade)	No data	Not flammable[h]	Not flammable[h]
Flashpoint	No data	Not flammable[h]	Not flammable[h]
Flammability limits	No data	Not flammable[h]	Not flammable[h]
Conversion factor:			
Solid	Not applicable	mg $ZnCl_2 \times 0.48$ = mg Zn	mg $ZnSO_4 \times 0.40$ = mg Zn
Explosive limits	No data	No data	No data

[a]All information obtained from Merck 1983 except where noted
[b]Weast 1988
[c]ACGIH 1991
[d]HSDB 1986
[e]Baes and Sharp 1983
[f]Baes et al. 1984
[g]Gerritse et al. 1982
[h]Weiss 1986

AVG = average; Zn = zinc; $ZnCl_2$ = zinc chloride; ZnO = zinc oxide; ZnS = zinc sulfide; $ZnSO_4$ = zinc sulfate

TABLE 3-2. Physical and Chemical Properties of Zinc and Selected Compounds[a] *(continued)*

Property	Zinc sulfide (α)	Zinc sulfide (β)	Zinc oxide
Molecular weight	97.45	97.45	81.38
Color	Colorless hexagonal crystals[b]	Colorless cubic crystals	White/yellowish-white powder; hexagonal crystals
Physical state	Solid	Solid	Solid
Melting point	1,700±20℃[b]	No data	100℃ (decomposes)
Boiling point	1,185℃ at 1 atm	1,185℃ at 1 atm	No data
Density (g/cm ^{3})	3.98 at 20℃[b]; 4.087 at 25℃	4.102 at 25℃	5.607 at 20℃
Odor	No data	No data	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water (mg/L)	6.9 at 18℃[b]	6.5 at 18℃[b]	1.6 at 29℃[b]
Other solvent(s)	Very soluble in alcohol; soluble in dilute mineral acids; insoluble in acetic acid; insoluble in alkalies	Very soluble in alcohol; soluble in dilute mineral acids; insoluble in alkalies	Soluble in dilute acetic or mineral acids, ammonia, ammonium carbonate, fixed alkali hydroxide solution, and ammonium chloride[b]; insoluble in alcohol[b]
Partition coefficients:			
Kd (mL/g)	No data	No data	No data
Kow	No data	No data	No data
Koc	No data	No data	No data
Vapor pressure (mm Hg)	No data	No data	Not applicable
Henry's law constant	Not applicable	Not applicable	Not applicable
Autoignition temperature (Centigrade)	No data	No data	Not flammable[h]
Flashpoint	No data	No data	Not flammable[h]
Flammability limits	No data	No data	Not flammable[h]
Conversion factor:			
Solid	mg ZnS × 0.67 = mg Zn	mg ZnS × 0.67 = mg Zn	mg ZnO × 0.80 = mg Zn
Explosive limits	No data	No data	No data

4 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Zinc is widely distributed in nature, constituting 0.027% (by weight) of the earth's crust (Merck 1983), but it is usually not found as elemental zinc in nature (Lloyd and Showak 1984). The procedure used to mine zinc varies with the composition of the ore. The zinc is mined using both underground mining and open pit mining (Stokinger 1981).

The mined zinc ores retrieved from the mines are too low in zinc content for direct reduction to refined metal; thus, they are first concentrated. Production of concentrates requires crushing and grinding followed by gravity or magnetic methods of separation or flotation. These processes may be combined, depending on the complexity of the ore. A caustic-leach process is used to decrease the extent of metal loss during the concentration process. In this process, the metal is leached by caustic soda, the resulting electrolyte is purified with zinc dust and lime, and the zinc is electrodeposited. The crude zinc may be dissolved in sulfuric acid and purified by electrodeposition. Two processes are used to produce metallic zinc from the ore concentrates that are not subjected to caustic soda leaching. In one process, the ore concentrate containing zinc sulfide is roasted in the presence of air to produce zinc oxide, which is combined with coke or coal and retorted to approximately 1,100°C to produce metallic zinc. In the other process, the roasted zinc oxide is leached with sulfuric acid, and the solution is electrolyzed to produce zinc of >99.9% purity. The electrolytic processing of zinc is replacing smelting as the most commonly used process (Lloyd and Showak 1984; Stokinger 1981).

The 20 leading U.S. zinc-producing mines accounted for more than 97% of production, with the 5 leading mines accounting for 47%. Tennessee is the largest zinc-producing state, followed by Missouri, New York, Colorado, Alaska, Montana, and Idaho (DO1 1991). In 1989, three companies operated four primary zinc refineries (Zinc Corporation of America, Monaco, Pennsylvania; Zinc Corporation of America, Bartlesville, Oklahoma; Big River Zinc Corporation, Sauget, Illinois; and Jersey Miniere Zinc Co., Clarksville, Tennessee). Secondary zinc metal was produced at nine plants from scrap materials, with the Zinc Corporation of America's plant in Monaco, Pennsylvania, being the largest producer of secondary zinc (DOI 1991). Table 4-l summarizes the facilities that manufacture or process zinc in the United States. The information

TABLE 4-1. Facilities That Manufacture or Process Zinc (Fume or Dust)[a]

State[b]	Number of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
AL	21	0-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13
AR	11	0-9,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12
AZ	3	0.1-9	1, 2, 3, 5, 6, 8, 11, 13
CA	36	0.1-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
CO	2	0.1-9	9, 13
CT	6	1-999	1, 5, 8, 9, 10, 13
FL	8 (1)[e]	1-999	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 13
GA	9	1-9,999	1, 2, 3, 4, 5, 8, 9, 11, 12, 13
IA	12	0-99	1, 3, 5, 7, 8, 9, 12
IL	48 (1)[e]	0-9,999	1, 2, 3, 4, 5, 6, 8, 9, 10, 12, 13
IN	32 (2)[e]	0.1-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
KY	13 (1)[e]	0-9,999	1, 2, 3, 4, 5, 8, 9, 12
LA	7	0.1-999	1, 5, 6, 8, 10, 11
MA	8 (1)[e]	0.1-99	8, 9, 12
MD	8	1-99	2, 4, 8, 9, 10, 11
ME	3	10-99	9, 12
MI	27	0-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12
MN	11 (2)[e]	1-999	1, 5, 8, 9, 13
MO	18 (1)[e]	0.1-9,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12
MS	3	1-99	9
NC	15	0.1-9,999	2, 3, 7, 8, 9, 10
NE	3	10-999	8, 9
NH	1	10-99	8
NJ	14	1-49,999	1, 2, 3, 4, 5, 7, 8, 9, 10
NM	1	1-9	9
NV	1	10-99	11
NY	12	0.1-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11
OH	46 (6)[e]	0-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
OK	9	0.1-999	1, 3, 7, 8, 9, 10, 12, 13
OR	5	1-999	1, 5, 8, 9, 10
PA	31	0-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
PR	6	1-999	3, 8, 9, 11
RI	5	0.1-999	1, 3, 5, 9, 10
SC	13 (1)[e]	0.1-999	1, 4, 5, 8, 9, 10
SD	1	10-99	9
TN	13 (1)[e]	1-9,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13
TX	22 (1)[e]	0.1-999	1, 2, 3, 5, 6, 7, 8, 9, 10, 13
UT	1	50,000-99,999	1, 5, 6, 9
VA	13	0-999	1, 5, 8, 9, 11, 13
VT	1	10-99	9
WA	5	10-999	5, 7, 8, 9
WI	25 (1)[e]	0-99,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
WV	6	1-9,999	1, 2, 3, 5, 7, 8, 9, 10

[a]Derived from TRI90 (1992)
[b]Post office state abbreviations
[c]Data in TRI are maximum amounts on site at each facility.
[d]Activities/Uses:

1. produce
2. import
3. for on-site use/processing
4. for sale/distribution
5. as a byproduct
6. as an impurity
7. as a reactant
8. as a formulation component
9. as an article component
10. for repackaging only
11. as a chemical processing aid
12. as a manufacturing aid
13. ancillary or other use

[e]Number of facilities reporting "no data" regarding maximum amount of the substance on site.

in this table was obtained from the Toxics Release Inventory (TRI), and it summarizes the reported release data for 1991 (TR191 1993). However, this list does not include all facilities that manufacture or process zinc. Table 4-l also lists the maximum amounts of zinc that are present at these sites and the end uses of zinc. In 1989, approximately 278,900 metric tons were produced from domestic ores in the United States, valued at roughly $499,100,000. The estimated world production from mines in 1989 was 7,062,000 metric tons. The production of zinc decreased from 1985 to 1987, but increased from 1987 to 1989 (DOI 1991).

Zinc is available in many commercial forms, including ingots, lumps, sheets, wire, shot, strips, sticks, granules, granulated zinc (obtained when molten metal is poured into cold water), and powder (Merck 1983).

4.2 IMPORT/EXPORT

In 1989, approximately 712,000 metric tons of zinc were imported to the United States in slab, block, and bar forms, approximately 388,600 metric tons were imported as ores and concentrates, and 72,000 metric tons were imported as pigments and compounds. In 1989, the United States imported less ore and concentrate than in the previous 2 years; more blocks, bars, and slabs than in 1987; and less blocks, bars, and slabs than in 1988 (DO1 1991).

In 1989, an estimated 78,880 metric tons of ores and concentrates, 17,120 metric tons of zinc and zinc alloys, and 108,090 metric tons of waste and scrap were exported from the United States. In contrast, exports of ores and concentrates reached approximately 23,000 metric tons in 1985. In 1989, the United States exported the largest amount of zinc ores and concentrates to Canada, Belgium, and Japan (DOI 1988, 1991).

4.3 USE

Zinc is used most commonly as a protective coating of other metals. In addition, it is used in alloys such as bronze and brass, for the electrical apparatus in many common goods, and in organic chemical extractions and reductions. Alloys containing zinc and copper are used to make U.S. one-cent coins. Zinc salts have numerous applications and are used in wood preservation, catalysts, photographic paper, vulcanization acceleration for rubber, ceramics, textiles, fertilizers,

pigments, and batteries. Zinc chloride is a primary ingredient in smoke bombs used for crowd dispersal, in fire-fighting exercises (by both military and civilian communities), and by the military for screening purposes. Zinc chloride, zinc sulfate, zinc oxide, and zinc sulfide have dental, medical, and household applications. Zinc chloride and zinc sulfate are also used as herbicides (HSDB 1993). In pharmaceuticals, zinc salts are used as solubilizing agents in many drugs, including insulin (Lloyd 1984; Lloyd and Showak 1984; Merck 1983). Zinc is also utilized therapeutically in human medicine in the treatment of zinc deficiency (Elinder 1986).

4.4 DISPOSAL

Criteria for land treatment or burial (sanitary landfill) disposal practices are subject to significant revision (HSDB 1993). Zinc processing plants have attempted to limit releases to the environment by using techniques such as water re-use, control of particulate emissions, and filtration thickener overflow. In addition, liquid effluents are limed and allowed to settle so that zinc can precipitate out as the hydroxide (Lloyd and Showak 1984). Waste products containing zinc are also being used as a source of zinc for electrogalvanizing (Jolly 1988). Disposal procedures for spills include ferric hydroxide precipitation and cement-based fixation processes; the latter method is very effective in rendering zinc contaminants insoluble (Dawson and Mercer 1986). Unsalvageable zinc waste may be buried in an approved landfill. The maximum allowable concentration in effluent to sewers or streams is 1.0 ppm (HSDB 1993).

In 1989, EPA applied its revised interpretation of the Bevill Amendment (exclusion) to solid waste from the extraction, beneficiation, and processing of ores and minerals. The slag from the primary zinc processing is the only zinc-related waste remaining in the Bevill exclusion (DOI 1991).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Zinc is an element commonly found in the earth's crust. It is released to the environment both from natural and anthropogenic sources; however, releases from anthropogenic sources are greater than those from natural sources. The primary anthropogenic sources of zinc in the environment (air, water, soil) are related to mining and metallurgic operations involving zinc and use of commercial products containing zinc. Worldwide, releases to soil are probably the greatest source of zinc in the environment. The most important sources of zinc in soil are discharges of smelter slags and wastes, mine tailings, coal and bottom fly ash, and the use of commercial products such as fertilizers and wood preservatives that contain zinc. Zinc does not volatilize from soil. Although zinc usually remains adsorbed to soil, leaching has been reported at waste disposal sites. Zinc does not volatilize from water but is deposited primarily in sediments through adsorption and precipitation. Severe zinc contamination tends to be confined to areas near emission sources.

Zinc is capable of forming complexes with a variety of organic and inorganic groups (ligands). Biological activity can affect the mobility of zinc in the aquatic environment, although the biota contains relatively little zinc compared to the sediments. Zinc bioconcentrates moderately in aquatic organisms; bioconcentration is higher in crustaceans and bivalve species than in fish. Zinc does not concentrate in plants, and it does not biomagnify through terrestrial food chains.

There are few data regarding the speciation of zinc released to the atmosphere. Zinc is removed from the air by dry and wet deposition, but zinc particles with small diameters and low densities suspended in the atmosphere travel long distances from emission sources.

Zinc has been detected in air, surface water, groundwater, and soil; the frequency of detection and the concentrations are greatest near source areas (e.g., hazardous waste sites and industrial areas such as lead smelters). In a survey by the National Air Surveillance Network, the mean concentration of zinc in the air in the United States in 1977-1979 was 0.02-0.16 $\mu g/m^3$ for urban air compared to 0.01-0.05 $\mu g/m^3$ for rural air. The concentrations of zinc in the air of remote areas range from <0.003 to 0.027 $\mu g/m^3$. The mean concentrations of zinc in ambient water and drinking water range from 0.02 to 0.05 mg/L and from 0.01 to 0.1 mg/L, respectively. The

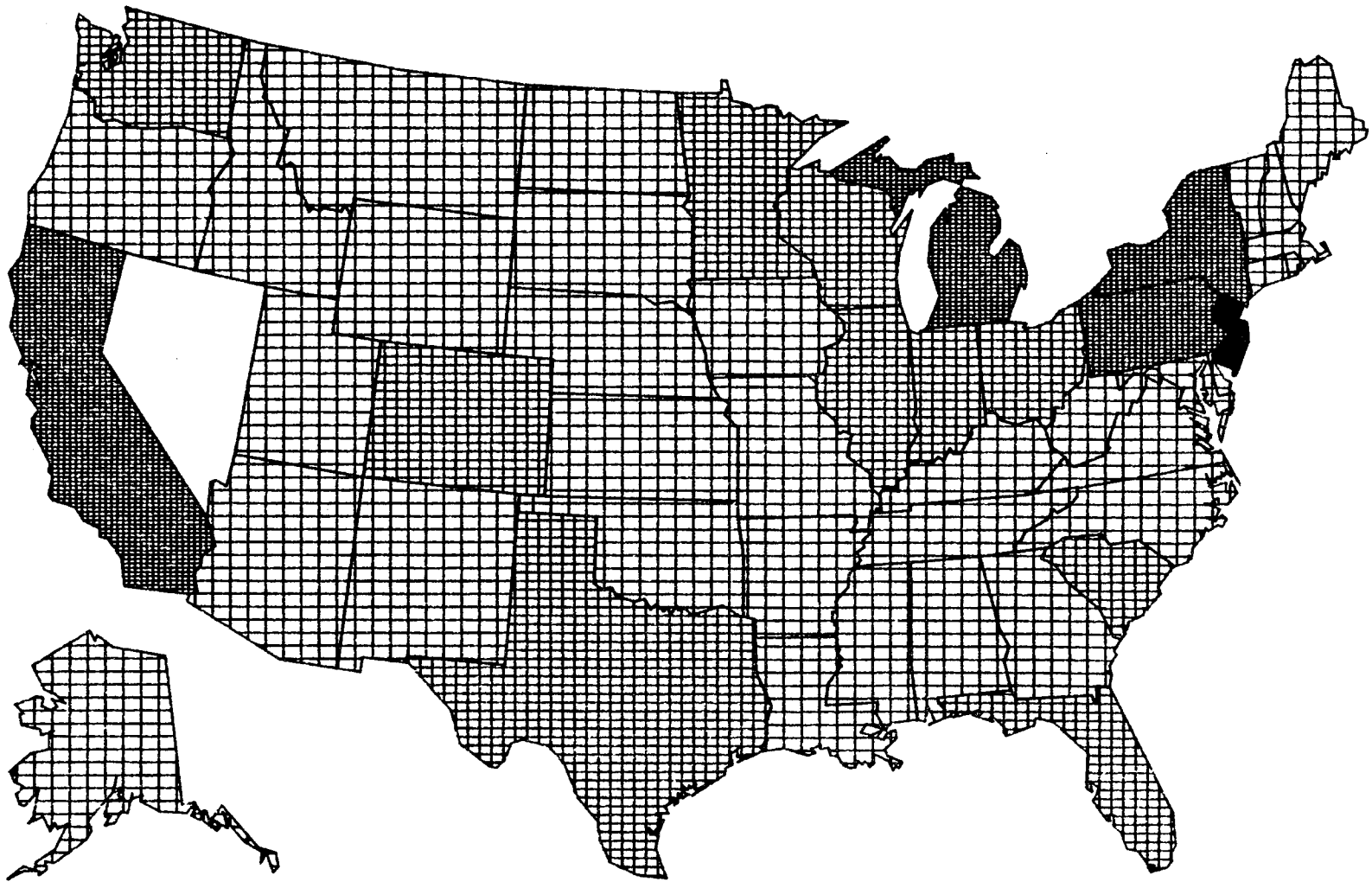
concentration of zinc in drinking water can often be higher than the concentration in the raw water from which the drinking water was obtained because zinc may leach from transmission and distribution pipes. The concentration of zinc in standing water from galvanized household water pipes was ≤1.3 mg/L (Sharrett et al. 1982a). The concentration of zinc in cultivated soils in the United States ranged from <5 to 400 mg/kg, with a mean of 36 mg/kg, compared to a range of <l0-2,000 mg/kg, with a mean of 51 mg/kg, in uncultivated soils; this probably results from the differences in soils used for farming rather than the use of zinc in agriculture. Concentrations of zinc can be high in soils from contaminated sites, such as waste dumps. Zinc has been identified in at least 776 of the 1,350 NPL hazardous waste sites (HAZDAT 1993). However, the number of sites evaluated for zinc is not known. The frequency of these sites can be seen in Figure 5-l. Seven sites are located in the Commonwealth of Puerto Rico (not shown).

The concentrations of zinc in various foods and human tissues have also been determined. In a 1980-1982 survey of total diet samples, the Food and Drug Administration (FDA) estimated that the average intake of zinc from food (including water) for an adult was 0.23 mg/kg/day. The FDA concluded that the daily intake of zinc from the inhalation of ambient air is negligible compared to the daily intake from food. Certain population groups may be exposed to higher concentrations of zinc than the general population. People who work in coal mines, people who work with the refining and smelting of nonferrous metals, and people who live near waste sites and metal smelting operations may be exposed to high levels of zinc. People who consume large amounts of foods high in zinc content, such as oysters and mussels, may also be exposed to high levels of zinc. The higher exposure may not always be manifested as increased body burden in the exposed individuals.

5.2 RELEASES TO THE ENVIRONMENT

Zinc is commonly found in the earth’s crust, and natural releases to the environment can be significant. In addition, zinc is one of the most widely used metals in the world. The major industrial sources of zinc include electroplating, smelting and ore processing, and drainage from both active and inactive mining operations (Mirenda 1986). Furthermore, zinc is an important component of brass, bronze, die casting metal, other alloys, rubber, and paints. The environmental releases of zinc from anthropogenic sources far exceed the releases from natural sources (Fishbein 1981).

FIGURE 5-1. FREQUENCY OF NPL SITES WITH ZINC CONTAMINATION *



*Derived from HazDat 1993

5.2.1 Air

Zinc is released to the atmosphere as dust and fumes from zinc production facilities, lead smelters, brass works, automobile emissions, fuel combustion, incineration, and soil erosion. Refuse incineration, coal combustion, smelter operations, and some metal-working industries constitute the major sources of zinc in air (EPA 1980d; Ragaini et al. 1977). Estimated atmospheric zinc loss is 100 g/ton of zinc mined, and most of the loss comes from handling raw and concentrated ore and wind erosion of tailing piles (Lloyd and Showak 1984). Average zinc emissions to the atmosphere from stationary sources in the United States were 151,000 tons/year for 1969-1971 (Fishbein 1981). An estimated projection of zinc emission for 1983, based on production estimates and assuming no changes in processes or control technology, was 273,000 tons/year. The estimated worldwide emission of zinc to the atmosphere in 1983 was 70,250-193,500 metric tons. Emissions from zinc-cadmium production, steel and iron manufacture, and copper-nickel production were estimated to be the principal atmospheric sources of zinc (Nriagu and Pacyna 1988). According to the TRI, an estimated total of 1,933,687 pounds of zinc, amounting to about 17% of the total environmental release, was discharged into the atmosphere in the United States in 1991 from the manufacturing and processing facilities listed in Table 5-l (TR191 1993). The TRI data should be used with caution since only certain facilities are required to report. Table 5-l is not an exhaustive list.

5.2.2 Water

Zinc and its compounds are found in the earth’s crust and are present in most rocks, certain minerals, and some carbonate sediments. As a result of the weathering of these materials, soluble compounds of zinc are formed and may be released to water (NAS 1977). The largest input of zinc to water results from erosion of soil particles containing natural traces of zinc (45,400 metric tons/year) (EPA 1980d). Erosion resulting from human activities accounts for 70% of this soil loss; geologic or natural erosion constitutes the other 30% (EPA 1980d). However, this source of low levels of zinc is widely dispersed and is, therefore, unlikely to elevate aquatic concentrations significantly.

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Zinc (Fume or Dust)[a]

State[c]	Number of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total Environment[d]	POTW[e] transfer	Off-site waste transfer
AL	21	0.0-39.1	0.0-0.0	0.0-0.3	0.0-49.5	0.0-83.2	0.0-0.8	0.0-13.0
AR	11	0.0-1.4	0.0-0.0	0.0-0.3	0.0-114.5	0.0-115.5	0.0-0.3	0.0-4.5
AZ	3	0.3-15.8	0.0-0.0	0.0-0.0	0.0-20.6	0.3-36.3	0.0-0.0	0.0-14.7
CA	36	0.0-7.6	0.0-0.0	0.0-0.0	0.0-0.0	0.0-7.6	0.0-0.3	0.0-24.0
CO	2	0.0-0.3	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.3	0.0-0.0	0.3-60.0
CT	6	0.0-8.4	0.0-0.0	0.0-0.3	0.0-28.5	0.0-37.2	0.0-0.0	0.0-124.4
FL	8	0.0-1.2	0.0-0.0	0.0-0.0	0.0-0.3	0.0-1.2	0.0-0.0	0.0-0.8
GA	9	0.0-12.0	0.0-0.3	0.0-0.8	0.0-67.0	0.0-79.0	0.0-0.0	0.0-27.0
IA	12	0.0-35.1	0.0-0.0	0.0-1.7	0.0-0.0	0.0-36.8	0.0-0.0	0.0-12.3
IL	48	0.0-145.0	0.0-0.0	0.0-2.2	0.0-2627.0	0.0-2773.8	0.0-1.7	0.0-321.8
IN	32	0.0-14.8	0.0-0.0	0.0-0.3	0.0-39.8	0.0-39.8	0.0-1.8	0.0-64.9
KY	13	0.0-20.7	0.0-0.0	0.0-3.9	0.0-2.8	0.0-25.8	0.0-0.3	0.0-357.7
LA	7	0.0-31.7	0.0-0.0	0.0-0.0	0.0-0.1	0.0-31.7	0.0-0.0	0.0-118.7
MA	8	0.0-1.0	0.0-0.0	0.0-0.3	0.0-0.0	0.0-1.3	0.0-0.3	0.0-3.5
MD	8	0.0-1.0	0.0-0.0	0.0-0.0	0.0-0.0	0.0-1.0	0.0-0.3	0.0-12.3
ME	3	0.0-2.8	0.0-0.0	0.0-0.0	0.0-0.0	0.0-2.8	0.0-0.0	5.9-15.5
MI	27	0.0-140.0	0.0-0.0	0.0-0.0	0.0-5880.0	0.0-5980.6	0.0-0.8	0.0-54.0
MN	11	0.0-22.7	0.0-0.0	0.0-0.0	0.0-0.0	0.0-22.7	0.0-2.5	0.0-11.3
MO	18	0.0-5.1	0.0-0.0	0.0-0.0	0.0-0.3	0.0-5.1	0.0-0.3	0.0-44.4
MS	3	0.0-0.0	0.0-0.0	0.0-0.0	0.0-10.0	0.0-10.0	0.0-0.1	0.0-0.8
NC	15	0.0-5.5	0.0-0.0	0.0-0.3	0.0-0.3	0.0-5.5	0.0-1.8	0.0-60.5
NE	3	0.1-6.9	0.0-0.0	0.0-0.0	0.0-0.0	0.1-6.9	0.0-0.0	0.0-0.3
NH	1	0.5-0.5	0.0-0.0	0.0-0.0	0.0-0.0	0.5-0.5	0.0-0.0	0.0-0.0
NJ	14	0.0-6.2	0.0-0.0	0.0-0.0	0.0-0.3	0.0-6.2	0.0-1.0	0.0-2833.2
NM	1	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.0	11.0-11.0	0.0-0.0
NV	1	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.0
NY	12	0.0-26.9	0.0-0.0	0.0-0.0	0.0-0.0	0.0-26.9	0.0-1.1	0.0-92.6
OH	46	0.0-27.1	0.0-0.0	0.0-0.3	0.0-3.3	0.0-27.3	0.0-1.3	0.0-2195.8
OK	9	0.0-4.6	0.0-0.0	0.0-0.0	0.0-0.3	0.0-4.6	0.0-0.4	0.0-1246.9
OR	5	0.0-45.7	0.0-0.0	0.0-0.1	0.0-0.3	0.0-45.7	0.0-0.0	0.0-0.8
PA	31	0.0-45.1	0.0-0.0	0.0-1.0	0.0-4.7	0.0-45.9	0.0-0.3	0.0-115.0
PR	6	0.0-0.3	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.3	0.0-2.0	0.0-8.5
RI	5	0.0-0.5	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.5	0.0-0.3	0.0-2.5
SC	13	0.0-68.7	0.0-0.0	0.0-0.0	0.0-0.3	0.0-68.7	0.0-0.3	0.0-92.0
SD	1	0.3-0.3	0.0-0.0	0.0-0.0	0.0-0.0	0.3-0.3	0.0-0.0	0.0-0.0
TN	13	0.0-133.0	0.0-0.0	0.0-2.8	0.0-2244.2	0.0-2379.9	0.0-0.3	0.0-16.1
TX	22	0.0-48.0	0.0-0.0	0.0-11.1	0.0-4.0	0.0-48.0	0.0-0.0	0.0-39.6
UT	1	36.7-36.7	0.0-0.0	0.0-0.0	0.0-0.0	36.7-36.7	0.0-0.0	119.7-119.7

TABLE 5-1 (continued)

State[c]	Number of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total Environment[d]	POTW[e] transfer	Off-site waste transfer
VA	13	0.0-102.0	0.0-0.0	0.0-4.3	0.0-18.0	0.0-102.0	0.0-0.3	0.0-169.7
VT	1	0.3-0.3	0.0-0.0	0.0-0.0	0.0-0.0	0.3-0.3	0.0-0.0	0.3-0.3
WA	5	0.0-24.2	0.0-0.0	0.0-0.0	0.0-0.0	0.0-24.2	0.0-0.0	0.0-1.9
WI	25	0.0-85.6	0.0-0.0	0.0-1.3	0.0-27.7	0.0-114.6	0.0-0.3	0.0-75.2
WV	6	0.0-19.3	0.0-0.0	0.0-0.0	0.0-0.0	0.0-19.3	0.0-0.0	0.0-6.8

[a]Derived from TRI90 (1992)
[b]Data in TRI are maximum amounts released by each facility. Quantities reported here have been rounded to the nearest hundred pounds, except those quantities > 1 million pounds which have been rounded to the nearest thousand pounds.
[c]Post Office state abbreviation
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility.
[e]POTW = publicly owned treatment works

Urban runoff, mine drainage, and municipal and industrial effluents are smaller but more concentrated sources of zinc in water. Industries that discharge large quantities of zinc directly to water include iron and steel, zinc smelting, plastics, and electroplating (EPA 1980d). The arithmetic mean concentration of zinc in influents of 239 waste-water treatment plants in the United States was 0.7 mg/L, with minimum and maximum concentrations of 0.0001 and 28.7 mg/L, respectively (Minear et al. 1981). Accidental zinc discharges to water are most often associated with smelting and refining operations. Zinc is present with cadmium and lead in these processes (NAS 1977). Urban runoff and drainage from inactive mines account for approximately 5,250 and 4,060 metric tons/year, respectively, of the total releases of zinc to water (EPA 1980d). Drainage from active mining areas is considerably less than from inactive areas because of the disposal methods currently employed. Hazardous waste sites, in which zinc has been improperly disposed of, are additional sources of the element.

Metals, such as zinc, also enter estuaries from many natural and man-made sources. Three important sources of zinc input into surface water are metal manufacturing, domestic waste water, and atmospheric fallout. On an annual worldwide basis, an estimated 77,000-375,000 metric tons of zinc are discharged into water from anthropogenic sources (Nriagu and Pacyna 1988). Publicly owned treatment works are the largest total point source for zinc discharges. Publicly owned treatment works receive zinc contributions from the water supply and distribution system corrosion, combined sewer area runoff, industrial wastes, and human excrement (EPA 1980d). According to the TRI, publicly owned treatment works discharged 30,466 pounds of zinc into the environment, whereas manufacturing and processing facilities listed in Table 5-l discharged an estimated 28,080 pounds of zinc (amounting to much less than 1% of the total environmental release) into surface waters in the United States in 1991 (TR191 1993). The TRI data should be used with caution since only certain types of facilities are required to report output. Table 5-l is not an exhaustive list.

The concentration of zinc in drinking water may increase as a result of the distribution system and household plumbing (EPA 1987~). Common piping materials used in distribution systems often contain zinc, as well as other metals and alloys. Trace metals may enter the water through corrosion products or simply by the dissolution of small amounts of metals with which the water comes in contact. Reactions with materials of the distribution system, particularly in soft low-pH waters, very often have produced concentrations of zinc in tap water much greater than those in

the raw or treated waters at the plant of origin (NAS 1977). The total quantity of annual releases of zinc from these sources has not been estimated.

5.2.3 Soil

Limited information is available on total releases of zinc to soil. Zinc is often present in soils and grasses as a result of atmospheric deposition. Furthermore, approximately 22,000 tons of zinc are used in fertilizers each year in the United States (NAS 1977). The extent to which zinc may run off into soil, rivers, and streams has not been evaluated. Hazardous waste sites are additional sources of zinc in soil. Municipal sludges applied to cropland soils can also be an important source of trace metals, including zinc (Chang et al. 1987).

On a worldwide basis, an estimated 1,193,000-3,294,000 metric tons of zinc per year are released to soil from anthropogenic sources (Nriagu and Pacyna 1988). The four most important sources of zinc in soil were estimated to be smelter slugs and wastes, mine tailings, coal and bottom fly ash, and the discharge of commercial products such as fertilizers. According to the TRI, an estimated total of 9,216,574 pounds of zinc, amounting to about 82% of the total environmental release in the United States, was released to soil in the United States in 1991 from the manufacturing and processing facilities listed in Table 5-l (TR191 1993). An estimated total of 115 pounds was released through underground injection, and another 73,000,000 pounds were transferred to off-site treatment, storage, and disposal facilities. The TRI data should be used with caution since only certain types of facilities are required to report. Table 5-l is not an exhaustive list.

5.3 ENVIRONMENTAL FATE

Zinc occurs in the environment mainly in the +2 oxidation state (Lindsay 1979). Sorption is the dominant reaction, resulting in the enrichment of zinc in suspended and bed sediments (Callahan et al. 1979). Zinc in aerobic waters is partitioned into sediments through sorption onto hydrous iron and manganese oxides, clay minerals, and organic material. The efficiency of these materials in removing zinc from solution varies according to their concentrations, pH, redox potential (Eh), salinity, nature and concentrations of complexing ligands, cation exchange capacity, and the concentration of zinc. Precipitation of soluble zinc compounds appears to be significant only

under reducing conditions in highly polluted water. Generally, at lower pH values, zinc remains as the free ion. The free ion (Zn^{+2}) tends to be adsorbed and transported by suspended solids in unpolluted waters. In polluted waters in which the concentration of zinc is high, removal of zinc by precipitation of the hydroxide is possible, particularly when the pH is greater than 8.0 (Callahan et al. 1979). In anaerobic environments and in the presence of sulfide ions, precipitation of zinc sulfide limits the mobility of zinc. The relative mobility of zinc in soil is determined by the same factors that affect its transport in aquatic systems (i.e., solubility of the compound, pH, and salinity) (Clement 1985).

Zinc is an essential nutrient that is present in all organisms. Although biota appears to be a minor reservoir of zinc relative to soils and sediments, microbial decomposition of biota in water can produce ligands, such as humic acids, that can affect the mobility of zinc in the aquatic environment through zinc precipitation and adsorption (Callahan et al. 1979).

Zinc concentrations in the air are relatively low, except near industrial sources such as smelters. No estimate for the atmospheric lifetime of zinc is available at this time, but the fact that zinc is transported long distances in air indicates that its lifetime in air is at least on the order of days.

5.3.1 Transport and Partitioning

The tendency of a chemical to partition between soil, water, sediment, air, and biota can be inferred from its physical and/or chemical properties. Zinc occurs in the environment primarily in the +2 oxidation state. It dissolves in acids to form hydrated Zn^{+2} cations and in strong bases to form zincate anions (probably $Zn[OH]_4^{-2}$). I n most unpolluted waters, zinc exists primarily as the hydrated form of the divalent cation. In polluted waters, the metal often forms complexes with a variety of organic and inorganic ligands (Callahan et al. 1979; EPA 1984b, 1987c).

Zinc can occur in both suspended and dissolved forms in surface water. Dissolved zinc may occur as the free (hydrated) zinc ion or as dissolved complexes and compounds with varying degrees of stability. Suspended (undissolved) zinc may be dissolved following minor changes in water chemistry or may be sorbed to suspended matter.

5. POTENTIAL FOR HUMAN EXPOSURE

In the aquatic environment, zinc partitions to sediments or suspended solids in surface waters through sorption onto hydrous iron and manganese oxides, clay minerals, and organic material. Reservoirs located downstream from lead-zinc mining and milling areas were found to contain higher concentrations of zinc than reservoirs in other areas, and the zinc was more highly concentrated in reservoir bottom sediments than in the surrounding soils (Pita and Hyne 1975). In addition, the zinc content in sediment closely correlated with the depth, organic content, and clay content of the sediments. Phosphates and iron hydroxides play an important role in the transfer of heavy metals (and presumably zinc) from river water to the sediments, according to a study by Houba et al. (1983). In this study, zinc was bound predominantly to carbonate and amorphous matter (iron, aluminum, and manganese hydroxides). In addition, mobile components of naturally occurring organic matter contributed to the increase in the metal hydroxide-bound fraction.

The transport of zinc in the aquatic environment is controlled by anion species. In natural waters, complexing agents, such as humic acid, can bind zinc. The stability of the zinc complex depends on the pH of the water and the nature of the complex. The dissociation of the complex may determine the amount of zinc in solution. Zinc in humic acid complex may be 50% dissociated at pH 5.5, and the dissociation rate may be higher as the pH decreases (Guy and Chakrabarti 1976). Therefore, as the pH of the water decreases, the concentration of zinc ions in the water phase increases at the same rate as that of the release of zinc from the sediment. The magnesium found in the silicate minerals of igneous rocks is often replaced with the divalent zinc ion; consequently, weathering of this zinc-containing bedrock gives rise to Zn^{+2} in solution. The hydrated cation is the dominant form when the pH is ≤9 (Callahan et al. 1979).

The tendency of zinc to be sorbed is affected not only by the nature and concentration of the sorbent but also by pH and salinity (Callahan et al. 1979). Zinc tends to sorb more readily at a high pH (pH >7) than at a low pH (Callahan et al. 1979). Desorption of zinc from sediments occurs as salinity increases (Helz et al. 1975), apparently because of displacement of the adsorbed zinc ions by alkali and alkaline earth cations, which are abundant in brackish and saline waters (Callahan et al. 1979). In column leaching tests with sediment collected from the banks of the Rhone River, the presence of dissolved organic matter and pH was found to be the factors controlling the adsorption and mobility of zinc (Bourg and Darmendrail 1992).

5. POTENTIAL FOR HUMAN EXPOSURE

A small fraction of the zinc initially exists in the aquatic phase as soluble inorganic zinc compounds. Zinc chloride and zinc sulfate are very soluble in water but hydrolyze in solution to form a zinc hydroxide precipitate. Hydrolysis may lower pH, but the buffering action present in most natural water prevents a significant alteration in pH. The precipitation of zinc hydroxide and zinc carbonate was studied by Patterson et al. (1977) who found that zinc hydroxide precipitates faster than zinc carbonate. Zinc carbonate is soluble in pure water at 25°C at concentrations of ≤107 mg zinc/L. The hydroxide is soluble only at concentrations of ≤0.2 mg zinc/L. As a result, some of the inorganic forms of zinc that are expected to be present in water are basic carbonate ($Zn_2[OH]_2CO_3$), hydroxide ($Zn[OH]_2$) and silicate (Zn_2SiO_4) (Florence 1980; NAS 1977). When the pH is ≥8, most of these compounds will precipitate; however, as the pH decreases, more and more of these compounds will dissolve and remain in the water phase (Callahan et al. 1979).

The effect of pH on the mobilization of zinc in a few highly acidic clean lakes has been studied (Sprenger et al. 1987; White and Driscoll 1987). In these lakes, in which the pH was ≤3.6, concentrations of zinc were elevated in the water column, and the concentration of zinc in the upper layer of sediment was substantially lower than values reported for other lakes at higher pH values. The relatively higher concentration of zinc in the water column compared to the sediment may be the result of lower adsorption of zinc on oxide surfaces due to low pH, solubilization of inorganic zinc from the sediment layer, and the dissociation of bound organic complexes of zinc present in the sediment and their subsequent release into the water phase.

The precipitation of zinc sulfide is an important control on the mobility of zinc in reducing environments where hydrogen sulfide is formed. The precipitation of the hydroxide, carbonate, or basic sulfate may become more significant at high concentrations in highly polluted water. The hydroxides and hydrous oxides of iron and manganese are often components of the clay fraction of sediments and often exist as coatings on the surfaces of other minerals (NAS 1977). Zinc may coprecipitate with hydrous oxides when reduced iron or manganese oxides are oxidized. As the new solids are formed, they can trap various ions in their crystal lattice (Callahan et al. 1979).

Zinc sorbs strongly onto soil particulates. Little water-soluble and exchangeable heavy metals were found in soil irrigated with raw waste water (Schalscha et al. 1982). Although considerable amounts of metals were added to the soil in soluble and exchangeable forms during waste-water

irrigation, they were converted into the less chemically active forms (i.e., organically bonded and inorganic precipitates). Further examination showed that zinc accumulation in soil resulting from waste disposal occurred primarily in inorganic precipitates.

The mobility of zinc in soil depends on the solubility of the speciated forms of the element and on soil properties such as cation exchange capacity, pH, redox potential, and chemical species present in soil; under anaerobic conditions, zinc sulfide is the controlling species (EPA 1980d; Kalbasi et al. 1978). Since zinc sulfide is insoluble, the mobility of zinc in anaerobic soil is low. In a study of the effect of pH on zinc solubility, Saeed and Fox (1977) showed that, when the pH is <7, an inverse relationship exists between the pH and the amount of zinc in solution. As negative charges on soil surfaces increase with increasing pH, additional sites for zinc adsorption are activated and the amount of zinc in solution decreases. The active zinc species in the adsorbed state is the singly charged zinc hydroxide species (i.e., $Zn[OH]^{+}$) (Sanders and Kherbawy 1987). Other investigators have also shown that the mobility of zinc in soil increases at lower soil pH under oxidizing conditions and at a lower cation exchange capacity of soil (Bergkvist et al. 1989; Hermann and Neumann-Mahlkau 1985; Tyler and McBride 1982). On the other hand, the amount of zinc in solution generally increases when the pH is >7 in soils high in organic matter. This is probably a result of either the release of organically complexed zinc, reduced zinc adsorption at higher pH, or an increase in the concentration of chelating agents in soil (Saeed and Fox 1977). For calcareous soils, the relationship between zinc solubility and pH is nonlinear. At a high pH, zinc in solution is precipitated as $Zn(OH)_2$, zinc carbonate ($ZnCO_3$), or calcium zincate (Saeed and Fox 1977). Clay and metal oxides are capable of sorbing zinc and tend to retard its mobility in soil. Soil distribution constants (K_d) of 100±770 mL/g for sandy loam soil and 0.2±4 mL/g for sandy soils were reported by Gerritse et al. (1982). A K_d of 0.1±8,000 mL/g was reported by Baes and Sharp (1983), but an average K_d of 40 mL/g was reported by Baes et al. (1984).

Zinc in a soluble form, such as zinc sulfate, is fairly mobile in most soils. However, relatively little land-disposed zinc is in the soluble form, and mobility is, therefore, limited by a slow rate of dissolution. Consequently, movement towards groundwater is expected to be slow unless zinc is applied to soil in soluble form (such as in agricultural applications) or accompanied by corrosive substances (such as in mine tailings) (EPA 1980d). Yet, soil conditions not suitable for zinc

sorption may lead to leaching. Low pH (pH <7) and high ionic strength of the leaching solution favor desorption (EPA 1987c; Saeed and Fox 1977).

Zinc is an essential nutrient and occurs in the tissues of organisms, even at normal ambient water and soil concentrations. Zinc can accumulate in freshwater animals at 51-1,130 times the concentration present in the water (EPA 1987c). Microcosm studies indicate, in general, that zinc does not biomagnify through food chains (Biddinger and Gloss 1984; Callahan et al. 1979; Hegstrom and West 1989). Furthermore, although zinc actively bioaccumulates in aquatic systems, biota appears to represent a relatively minor sink compared to sediments. Steady-state zinc bioconcentration factors (BCFs) for 12 aquatic species range from ≈4 to 24,000 (EPA 1987c). Crustaceans and fish can accumulate zinc from both water and food. A BCF of 1,000 was reported for both aquatic plants and fish, and a value of 10,000 was reported for aquatic invertebrates (Fishbein 1981). The order of enrichment of zinc in different aquatic organisms was as follows (zinc concentrations in μg/g dry weight appear in parentheses): fish (23, shrimp (50), mussel (60), periphyton (260), zooplankton (330), oyster (3,300) (Ramelow et al. 1989). The high enrichment in oysters may be due to their ingestion of particulate matter containing higher concentrations of zinc than does ambient water. Other investigators have also indicated that organisms associated with sediments have higher zinc concentrations than organisms living in the aqueous layer (Biddinger and Gloss 1984). With respect to bioconcentration from soil by terrestrial plants, invertebrates, and mammals, BCFs of 0.4, 8, and 0.6, respectively, have been reported. The concentration of zinc in plants depends on the plant species, soil pH, and the composition of the soil (Dudka and Chlopecka 1990; Rudd et al. 1988). Plant species do not concentrate zinc above the levels present in soil (Levine et al. 1989).

Wind-blown dust transports zinc bound to soil particulates into the atmosphere (EPA 1980d). The particulates may also contain other materials (Pacyna et al. 1989; Saltzman et al. 1985). Zinc-bearing particles in the atmosphere are transported to soil and water by wet deposition (rain and snow) and dry deposition (gravitational settling and deposition on water and soil surfaces). The detection of zinc in rainwaters (at concentrations higher than atmospheric particles) confirms the importance of wet precipitation in the removal of zinc particles from the atmosphere (Aten et al. 1983; Colin et al. 1990; Dasch and Wolff 1989; Heaton et al. 1990). Zinc particles with low dry deposition velocities (i.e., particles with small diameters and low densities) can be transported from their emission source to distant regions (Pacyna et al. 1989).

5.3.2 Transformation and Degradation

The transformation of zinc compounds can occur as a result of changes in chemical speciation, such as the formation of zinc oxide in the atmosphere, the hydrolysis of hydrated zinc cations, or the oxidation/reduction of organic and inorganic zinc complexes.

5.3.2.1 Air

The chemical interaction of zinc compounds in the atmosphere may change the anionic speciation of the compound. Atmospheric interactions are greatest for particles with small aerodynamic diameters (Fishbein 1981). Zinc is found in the atmosphere at the highest concentrations in the smallest particles (Fishbein 1981). Atmospheric emissions of zinc, consisting primarily of zinc sorbed to submicron particulate matter in the form of zinc oxide, are expected to dissipate quickly as a result of deposition to soil and surface waters (EPA 1980d).

In the atmosphere, zinc-bearing particles may undergo chemical transformation before deposition. The association of zinc particles in aerosols in Arizona was studied, and five zinc-bearing particles were identified with an automated scanning electron microscope (Anderson et al. 1988). These particles, in decreasing order of concentration in the aerosol, were zinc sulfide, ferrous zinc, zinc phosphides, zinc chloride, and metallic zinc. The presence of zinc sulfide in an area adjacent to mining and smelting activities is not surprising, but no conclusion regarding the speciation of zinc in the atmosphere can be drawn from this investigation. However, the relative concentration of zinc ions in rainwater from a rural area was one order of magnitude higher than in airborne particulates (Aten et al. 1983). This finding suggests that zinc sulfide in the atmosphere is oxidized to a more water-soluble form, zinc sulfate.

5.3.2.2 Water

Zinc is in the +2 form in aqueous solution and exhibits amphoteric properties; it dissolves in acids to form hydrated Zn^{+2} cations and in strong bases to form zincate anions (probably $Zn[OH]_4^{-2}$) (Callahan et al. 1979). However, at the pH of most natural waters, the formation of anionic zinc species is not likely.

A small part of the available zinc may partition into the aquatic phase through the formation of soluble zinc chloride and sulfate compounds. These compounds hydrolyze in solution to form the hydroxide or hydrated zinc oxide precipitate with the resultant decrease in pH. The decrease in pH may increase the solubility of zinc hydroxide and increase the zinc concentration in water. However, the buffering action of most natural waters prevents any significant change of pH due to the hydrolysis reactions. As a result, in the water phase, the solubility of its carbonate and hydroxide is likely to control the availability of zinc. It was reported by Patterson et al. (1977) that $Zn(OH)_2$ precipitates faster than $ZnCO_3$. Zinc is not directly affected by changes in Eh; however, the valences and reactivity of ligands reacting with zinc are affected by Eh. Zinc is an active reducing agent for many ions such as iron ($Fe+^3$) and permanganate (MnO_4^{-2}) ions (Stokinger 1981). As a result of the reducing reactions, the manganese oxides and ferric salts may precipitate out and, in the process, may entrap soluble zinc in the precipitate, thereby reducing the zinc concentration in the water phase.

Because alkyl zinc compounds are unstable in water and oxygen, biomethylation of zinc compounds in aquatic ecosystems probably does not occur (Callahan et al. 1979). No evidence was found that photolysis in the aquatic environment significantly affects the fate of zinc compounds.

5.3.2.3 Sediment and Soil

No information specifically related to transformation and degradation in sediment and soil was identified in the available literature. However, chemical speciation of zinc in sediment and soil is probably affected by the same factors affecting its fate in water. The sediment and soil chemistry of zinc are governed primarily by the pH and the physical properties of sediment and soil. In acidic sediments and soils, more zinc is available in ionic forms, and cation exchange processes influence its fate. Depending on the nature and concentrations of other mobile metals in sediments and soils, competition for the binding sites probably occurs. In the absence of suitable binding sites, zinc may be mobilized (ICF 1986). In alkaline soils, the chemistry of zinc is dominated by interactions with organic ligands.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Zinc concentrations in air are relatively low and fairly constant except near sources such as smelters. Average atmospheric concentrations of zinc resulting from releases from automobiles, fuel combustion, incineration, soil erosion, and industrial, commercial, and construction activity throughout the United States generally are less than 1 μg/m^3 (EPA 1980d; Lloyd and Showak 1984). Data on zinc concentrations in New York City during 1972-1975 show that the average atmospheric zinc concentration ranged from 0.293 to 0.380 pg/m^3 annually (Lioy et al. 1978). An average ambient zinc concentration of 0.127 μg/m^3 (concentration range, 0.027-0.500 μg/m^3) was determined from analyses of particulate samples collected at nine air monitoring sites in the San Francisco Bay area (John et al. 1973). The concentrations of zinc in atmospheric samples collected from seven cities in the United States during 1968-1971 ranged from 0.17 to 0.67 μg/m^3, whereas the concentrations at two rural sites ranged from 0.02 to 0.16 μg/m^3 (Saltzman et al. 1985). The concentrations of zinc during 1977-1979 from the National Air Surveillance Networks were reported by Evans et al. (1984). The arithmetic mean zinc concentrations in urban areas in the United States ranged from 0.02 to 0.16 μg/m^3, whereas the concentrations in non-urban areas ranged from 0.01 to 0.05 μg/m^3. The geometric mean concentrations of zinc from three urban areas in New Jersey monitored more recently (1981-1982) ranged from 0.07 to 0.59 μg/m^3, whereas the concentrations at a rural site ranged from 0.02 to 0.06 μg/m^3 (Daisey 1987). The reported concentration range of zinc in air at remote sites (arctic) was <0.003-0.027 μg/m^3 (Barrie and Hoff 1985; Duce et al. 1975; Zoller et al. 1974). In aerosol samples of the lower troposphere collected over the Southern Bight of the North Sea between September 1988 and October 1989, the average zinc concentration was 67 ng/m^3 (standard deviation, 54 ng/m^3; range, 3-220 ng/m^3; n = 108 samples) (Injuk et al. 1992). The concentration of atmospheric zinc is usually lower in winter than in summer (Barrie and Hoff 1985; Daisey 1987).

Although data are sparse, higher-than-background concentrations have been reported near ironand steel-producing factories and zinc, lead, and copper smelters. During zinc smelting operations, concentrated zinc ore goes through a roasting procedure to convert zinc sulfide to zinc oxide. This process accounts for a large portion of the total atmospheric zinc emission during primary production (EPA 1980d). About 1.5 miles from a smelter in Kellogg, Idaho, Ragaini

al. (1977) detected high annual mean concentrations of zinc in ambient air of 5 μg/m^3. The 24-hour values for zinc ranged from 0.27 to 15.7 μg/m^3; the average lead and cadmium concentrations at this smelter site were 11 and 0.8 μg/m^3, respectively, indicating severe environmental pollution. Higher concentrations of zinc in the vicinity of a copper smelter than in reference areas were also reported by Patterson et al. (1977).

5.4.2 Water

In general, zinc is more concentrated in the sediments of streams and rivers than in the water column. It is reported by NAS (1977) that zinc will probably be detected in 75% of all water samples examined for zinc from various locations.

The zinc background concentrations in surface waters are usually less than 50 μg/L (EPA 1980d), but concentrations in different surface waters and groundwater can range from 0.002 to 50 mg/L (NAS 1977). In many locations (e.g., New England, the southeast, the Missouri River basin, the Rio Grande River basin, and the Upper Colorado River basin), higher-than-background concentrations of zinc are common and appear to be correlated with mining activities in these areas and/or geological areas rich in zinc (EPA 1980d). However, in all river basins there are some locations with zinc concentrations of 0.1-1.0 mg/L (EPA 1980d).

The concentrations of zinc in water samples from Whitewood Creek, South Dakota, were measured by Hale (1977). The samples were collected upstream from the discharge of a local mining company. In 42 analyses, zinc concentrations ranged from <.004 to 0.048 mg/L with a mean concentration of 0.018 mg/L. The level of dissolved zinc in water from Lakes Erie and Ontario ranged from $3x10^{-6}$ to $1.1x10^{-4}$ mg/L (Coale and Flegal 1989).

Concentrations of zinc in surface water often correlate with the introduction of urban and industrial runoff. The Nationwide Urban Runoff Program (NURP), initiated to evaluate the significance of priority pollutants in urban storm water runoff, reports a frequency of detection for zinc of 95%, with a concentration range of 0.01-2.4 mg/L (Cole et al. 1984).

The concentrations of zinc in drinking water can be higher than concentrations in surface waters. Concentrations of 0.002-1.2 mg/L were detected in 77% of 1,577 surface water samples; levels of

0.003-2.0 mg/L were found in 380 drinking water samples (NAS 1977). The higher concentrations in drinking waters are due to water treatment and to the distribution systems used for the water. Zinc in drinking water at levels as great as several mg/L was due to galvanized pipes and tanks in alkaline-water distribution systems. For example, drinking water samples from galvanized pipe plumbing systems in Seattle, Washington, contained zinc concentrations of 0.128-1.279 mg/L; these levels were >l0 times higher than those in homes with copper pipe plumbing systems (Sharrett et al. 1982a). The results of analyzing 43 tap-water samples, collected in homes in Dallas, Texas, for trace metals reported maximum, minimum, median, and average concentrations of 0.049, 0.005, 0.011, and 0.0124 mg zinc/L, respectively (NAS 1977). The high zinc concentrations in these water samples were believed to be due to the household plumbing. In a study investigating associations between inorganic constituents of drinking water and cardiovascular diseases, Greathouse and Osborne (1980) collected and analyzed tap water samples in 35 geographic areas in the United States. From 100 to 110 tap-water samples were collected from each area. The maximum, minimum, and mean concentrations were 1.447, 0.025, and 0.144 mg zinc/L, respectively. Seventy-five percent of the zinc values were below 0.236 mg/L. Other investigators have also attributed the higher concentrations of zinc in household tap waters, compared to the raw originating water, to distribution and transmission lines (Maessen et al. 1985; Ohanian 1986; Schock and Neff 1988).

The available data suggest that zinc concentrations in drinking water are far less than the levels required to meet a daily intake level of 15 mg/day (assuming an adult water consumption of 2 L/day) (NAS 1977).

5.4.3 Sediment and Soil

Data on ambient concentrations of zinc in soil are limited. Zinc is generally found in soils at concentrations between 10 and 300 mg/kg, with a mean of ≈50 mg/kg (EPA 1980d). Zinc concentrations measured across the United Stated ranged from <5 to 400 mg/kg and from <10 to 2,000 mg/kg, with corresponding means of 36 and 51 mg/kg in cultivated and uncultivated subsurface soils, respectively (Connor and Shacklette 1975); however, these differences in zinc concentration may be attributed to differences in the soils prior to use (and not to cultivation). The sampling survey was designed to determine zinc concentrations of surficial materials unaltered from their natural condition. Soils near highways and smelters contained high zinc concentrations

as a result of deposition of zinc released in tire abrasion and stack emissions (EPA 198Od). A study was designed by Hutchinson and Wai (1979) to investigate the distribution of cadmium, lead, and zinc in the soil and vegetation grown on it at two reclaimed waste dumps from phosphate ore mines in southeastern Idaho. Zinc concentrations in the soil of the waste dumps averaged from 443±210 to 1,112±124 mg/kg. These values were high compared with those found in the control plot (54216 mg/kg). Zinc concentrations in vegetation from the reclaimed waste dumps were also high compared to the control plot. Moderate-to-high levels of zinc contamination were found in leafy vegetables (lettuce) and their supporting soil in a zone with a 0-5-km radius around a copper smelter (Beavington 1975). The mean concentrations of zinc in 17 soil samples and 12 lettuce samples collected in this zone were 229±17 and 316±64 mg/kg dry weight, respectively. Significant relationships were found between the distance from the smelter and the levels of easily extractable zinc in the soil, and between the distance from the smelter and the content of zinc in herbage. Concentrations of zinc in soil irrigated with waste water or river water were measured by Schalscha et al. (1982). The total concentration of zinc in waste-watertreated soils was 228 mg/kg. The total concentration of zinc in soils irrigated with river water ranged from 103 to 136 mg/kg.

Municipal sludge and municipal incineration ash contain considerably higher levels of zinc than uncontaminated soils (Mumma et al. 1984, 1990, 1991). Therefore, application of sludge and municipal ash to soil will elevate the levels of zinc in these soils. The mean concentrations (mg/kg) of zinc according to four land use types were as follows: agricultural, 25; suburban residential, 75; mixed industrial/residential, 157; and industrial inner urban area, 360 (Haines 1984).

Since zinc in water is transported to the sediment in the adsorbed or precipitated state, the concentration of zinc in sediments of most waters is higher than the zinc concentration in aqueous phase. The concentration of zinc in Hamilton Harbor sediments ranged from 1,050 to 2,900 mg/kg, compared to zinc concentrations of 6-48 μg/L in the aqueous phase (Mayer and Manning 1990). The concentrations of zinc in sediments of upper Columbia River, British Columbia, ranged from 45 to 51 mg/kg, while zinc concentrations in sediments from Lake Roosevelt, Washington, were 60-26,840 mg/kg (Johnson et al. 1990). The higher zinc concentrations in lake sediments were due to discharges from a lead-zinc smelter and a refinery. In the sediments of eight remote lakes in the Adirondack region of the northeastern United

States, zinc concentrations in sediment cores ranged from 550±140 mg/m^2 to 5620±2680 mg/m^2 (Kada and Heit 1992).

5.4.4 Other Environmental Media

Bivalves and other sessile estuarine organisms are often used as a measure of contamination of estuarine water because they usually contain higher levels of metals than fish. The arithmetic mean concentration of zinc in oysters (Crassostrea virginica) from the Mississippi Sound collected in 1988 was 640 mg/kg (wet weight) (Lytle and Lytle 1990). In a nationwide mussel watch program, the mean concentrations of zinc in molluscs (*Mytilus edulis*) around the coast of the United States during 1976-1988 ranged from 67 to 3,700 mg/kg (dry weight) (Lauenstein et al. 1990). Although the concentration on a nationwide basis varied depending on sampling sites, the level of zinc showed little evidence of statistically significant change during 1976-1988. The mean concentration of zinc in oysters (*Crassostrea virginica*) collected from the U.S. coastline of the Gulf of Mexico during 1986-1988 was 2,150 mg/kg (dry weight) (Presley et al. 1990). In the National Contaminant Biomonitoring Program, the geometric mean concentration of zinc in various whole fish was 21.7 mg/kg (wet weight) (Schmitt and Brumbaugh 1990). Of all fish tested (e.g., bloater, sucker, white perch, bass, catfish, etc.), common carp showed the highest level of zinc. No significant trend in the level of zinc in whole fish was observed during 1978-1984. The concentration of zinc in yellow perch (*Perca flavescens*) from six acidic lakes in northwestern New Jersey ranged from 26.1 to 66.2 mg/kg (dry weight) (Sprenger et al. 1988). Although the concentrations of mercury and lead in fish from acidic lakes were higher compared to fish collected from non-acidic lakes, the concentrations of zinc showed no significant difference. Similarly, high concentrations of zinc were not found in white suckers (*Catostomus commersoni*) and brown bullheads (*Ictalurus nebulosus*) collected from two acidic Adirondack lakes in New York (Heit and Klusek 1985).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Zinc is ubiquitous in living organisms and ranks as one of the most abundant trace metals in humans. Humans are primarily exposed to zinc through ingestion. Sources of exposure include drinking water, food, air that is polluted, tobacco products, and occupational exposure. An average intake in humans is on the order of 0.14-0.21 mg zinc/kg/day (NAS 1977). The dietary

intake of an average teenage male has been estimated to be so ≈0.27 mg zinc/kg/day, and dietary supplements may provide up to an additional 1 mg zinc/kg/day (EPA 1980d). In an extensive survey of foods in the total diets of individuals in the United States, conducted by the FDA during 1982-1984, the following values for daily zinc intakes (mg/day) were estimated in eight age and sex groups: 6-ll-month-old infants, 5.24; 2-year-old children, 7.37; 14-16-year-old girls, 9.90; 14-16-year-old boys, 15.61; 25-30-year-old women, 9.56; 25-30-year-old men, 16.15; 60-65-yearold women, 8.51; and 60-85-year-old men, 12.64 (Pennington et al. 1986). Based on a body weight of 70 kg for a 25-30-year-old man, the intake corresponds to 0.23 mg/kg/day. The FDA included drinking water in the total diet. In a review of the literature, the National Research Council concluded that zinc concentrations in drinking water are generally well below 5 mg/L (NAS 1977). Assuming a daily intake of 2 L of water and an average body weight of 70 kg, a daily intake of less than 0.14 mg zinc/kg/day from drinking water can be estimated. Based on a body weight of 70 kg, the mean daily intakes of zinc in drinking water for residents of homes with galvanized and copper pipe plumbing systems in Seattle, Washington, were estimated to be 0.017-0.028 and 0.002-0.006 mg/kg/day, respectively (Sharrett et al. 1982b).

The NAS established the RDAs for zinc at 15 mg/day for men and 12 mg/day for women (NAS/NRC 1989b). The major source of zinc for the general population is food (EPA 1987~). Zinc is widespread in commonly consumed foods but tends to be higher in those of animal origin, particularly some seafoods (e.g., one serving of oysters will more than meet the daily dietary requirements of zinc) (NAS/NRC 1979). Meat products contain relatively high concentrations of zinc, whereas fruits and vegetables have relatively low concentrations. Generally, a person must eat a fairly high-protein diet to meet the RDA for zinc. Meats, fish, and poultry contained an average of 24.5 mg zinc/kg, whereas grains (or cereal products) and potatoes contained 8 and 6 mg/kg, respectively (Mahaffey et al. 1975). Zinc was present in all of the examined food classes. A diet of dairy products, meat, fish, poultry, grains, and cereals provides approximately 77% of the daily zinc intake. More recent data reported by the Food Safety and Inspection Service of the U.S. Department of Agriculture indicate that zinc was detected in 99.4-100% of the samples of healthy livestock and poultry randomly selected from among the specimens presented for slaughter in 1985-1986. Zinc concentrations in muscle tissue ranged from 0.20 ppm in young turkeys (n=61) to 1.92 ppm in heifers/steer (n=287) (Coleman et al. 1992). In a review of zinc levels in vegetables and other foods and beverages of plant origin, Weigert (1991) reported the following average concentrations (mg/kg): wheat - 41; rye - 13; rice - 8-20; potatoes - 3.51;

vegetables - 4.31; fruit - 1.66; mushrooms - 9.7; cocoa - 35; tea - 35; and coffee - 6.7. Zinc has also been detected in wines from Seville, Spain, at concentrations of 0.3-5.40 pg/mL (Lopez-Artiquez et al. 1990). The FDA collected samples of foods representative of adult diets in 27 cities between October 1980 and March 1982 as part of its Total Diet Studies program (Gartrell et al. 1986a). Individual food items were separated into a number of food groups, and each was analyzed as a composite sample. The results for each food group were as follows:

Food Group	Average Concentration (ppm)	Average Intake (mg/day)
Dairy products	4.57	3.47
Meat, fish, and poultry	29.20	7.67
Grain and cereal products	8.68	3.64
Potatoes	4.82	0.77
Leafy vegetables	2.26	0.12
Legume vegetables	8.27	0.60

Federal regulations permit the use of zinc acetate, zinc oxide, and zinc sulfide as components of adhesives, coatings, or rubber packaging materials intended for food contact (FDA 1987b, 1987c, 1987d). Federal regulations also permit the use of zinc chloride, zinc oxide, zinc stearate, and zinc sulfate as GRAS (Generally Recognized As Safe) food additives when they are used “in accordance with good manufacturing practices” (FDA 1987e, 1987f, 1987g, 1987h, 1987i, 1987j). In addition, the use of zinc oxide as a color additive in drugs and cosmetics is also permitted with certain restrictions (FDA 1987a).

Negligible quantities of zinc are inhaled in ambient air. Exposure to airborne zinc is largely occupational through the inhalation of industrial dusts or fumes. Individuals occupationally exposed to metallic zinc and zinc compounds are those involved in galvanizing, smelting, welding, or brass foundry operations. In such operations, zinc as ore or metal and its alloys are often exposed in an oxidizing atmosphere to temperatures near the metal’s boiling point of 907°C. This heating results in the formation of fresh zinc oxide particles (0.2-1.0 μm), which may subsequently be inhaled. Inhalation of zinc oxide particles and fumes by workers can result in metal fume

fever. Inhalation was reported to be the most probable route of exposure to zinc for 26 lead smelter workers found to have significantly ($p<0.01$) elevated blood plasma levels of zinc. Mean plasma zinc concentrations were 12.9 mmol/L (range, 9.8-16.7) for the workers versus 10.9 mmol/L (range, 8.1-14.6) for a non-lead-exposed control group (Vasikaran et al. 1992).

Data from the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicate that 269 workers (including 22 women) in 22 plants were potentially exposed to pure zinc, and 133,608 workers (including 17,586 women) in 6,157 plants were potentially exposed to other forms of zinc (unknown composition) in the workplace in 1980 (NIOSH 1984b). All of the workers exposed to pure zinc were employed in the fabricated metal products industry as millwrights or assemblers. The largest numbers of workers exposed to other forms (unknown composition) of zinc worked in the primary metal industries, with fabricated metal products, with transportation equipment, with stone, clay, and glass products, and in special trade contractors industries. The occupational groups with the largest numbers of exposed workers were miscellaneous machine operators (not elsewhere classified or not specified), molding and casting machine operators, janitors and cleaners, and machinists. Exposure estimates were derived from observations of the actual use of the compound and the use of trade name products known to contain the compound.

The mean concentration of zinc in the fingernails and toenails of populations from the United States, Canada, and Japan were 105, 109, and 94 mg/kg, respectively (Takagi et al. 1988). The geometric mean concentrations of zinc in toenails (129 mg/kg) and scalp hair (108 mg/kg) of preschool
children in Germany were about the same (Wilhelm et al. 1991). The total concentrations of zinc in 29 body tissues of 55 human cadavers were measured (Saltzman et al. 1990). The lowest concentration (mean of 1.5±2.2 mg/kg [wet weight]) of zinc in both males and females was found in adipose tissues, while the highest concentrations were detected in the skull of males (mean of 54.3 mgkg [wet weight]) and in the skeletal muscle of females (mean of 59.0 mg/kg [wet weight]). The mean concentrations of zinc in the feces of low-income urban Hispanics and rural Blacks in the United States were 75 and 94 mg/kg (wet weight), respectively (Prevost et al. 1985).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Certain populations receive greater-than-average exposures to zinc from environmental sources. For example, higher levels of zinc have been reported in soil and water near waste sites, metal smelters, and areas exposed to untreated waste water (Hutchinson and Wai 1979; Ragaini et al. 1977; Schalscha et al. 1982). Other populations at risk of high exposure are those that have galvanized plumbing in their residences, and those that intentionally consume large doses of zinc as a dietary supplement. Patients who receive chronic treatment with drugs containing zinc salts (such as injectable insulin) are exposed to higher zinc levels than the general population. Allergic reactions to the zinc in insulin have been reported (Bruni et al. 1986). People in certain occupations are likely to be exposed to higher concentrations of zinc than the general population (see Section 5.5). However, the higher exposure may not be indicative of a long-term increase in body burden. For example, the median zinc concentration in the lung tissues of 21 Swedish workers previously employed in the refining and smelting of nonferrous metals was about the same as in a control group (11.0 versus 10.7 mg/kg [wet weight]) (Hewitt 1988). On the other hand, the median concentration of zinc in lung tissues of eight deceased coal miners from England was 72 mg/kg (wet weight) compared to a median value of 54 mg/kg (wet weight) for a control group (Hewitt 1988); however, the study author did not provide any evidence that the difference in zinc concentrations in the lungs of unexposed controls is statistically significant.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of zinc is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of zinc.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the

identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The available data adequately characterize the physical and chemical properties of the various forms of zinc to permit estimation of their environmental fate (ACGIH 1991; Baes and Sharp 1983; Baes et al. 1984; Gerritse et al. 1982; HSDB 1986, 1990; Merck 1983; NIOSH 1990; Weast 1988; Weiss 1986).

Production, Import/Export, Use, and Disposal. Zinc is a metallic element commonly found in ores in the earth's crust, and natural releases to the environment can be significant. Zinc is also one of the most widely used metals in the world (Mirenda 1986). In 1989, approximately 278,900 metric tons were produced from domestic ores in the United States (DOI 1991). The estimated world production from mines in 1989 was 7,062,000 metric tons. The production of zinc decreased from 1985 to 1987 but increased from 1987 to 1989 (DO1 1991). No estimates were located regarding current production. Zinc is most commonly used as a protective coating for other metals. It is also used in alloys such as bronze and brass, for electrical apparatus, and in organic chemical extractions. Zinc salts have numerous applications, including wood preservation. Zinc chloride is a primary ingredient in smoke bombs. In pharmaceuticals, zinc salts are used as solubilizing agents in drugs, including insulin (Lloyd 1984; Lloyd and Showak 1984; Merck 1983). Zinc oxide is found in ointments used to treat burns and infectious and skin diseases (EPA 1987d). Zinc is also utilized therapeutically in human medicine in the treatment of zinc deficiency (Elinder 1986). Zinc is also a food contaminant (EPA 1987~). The primary anthropogenic sources of zinc in the environment (air, water, soil) are related to mining and metallurgic operations involving zinc and use of commercial products containing zinc (EPA 198Od; NAS 1977; Nriagu and Pacyna 1988; Ragaini et al. 1977; TRI91 1993). Zinc has been detected in air, surface water, groundwater, and soil, with the frequency of detection and the concentrations greatest near source areas (e.g., hazardous waste sites and industrial areas such as lead smelters) (EPA 1980d; HAZDAT 1993; Lioy et al. 1978; Lloyd and Showak 1984; Mumma et al. 1984, 1990, 1991; NAS 1977). Current disposal methods are efficient (Dawson and Mercer 1986; Lloyd and Showak 1984). No data were located regarding the amount of zinc being disposed. There are rules and regulations regarding the disposal of zinc (Dawson and Mercer 1986; DO1 1991).

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 USC. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1991, became available in May of 1993. Environmental releases of zinc from manufacturing and processing facilities required to report their releases are listed in Table 5-1. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Zinc partitions to the air, water, and soil (Callahan et al. 1979; Guy and Chakrabarti 1976; Houba et al. 1983; Pita and Hyne 1975). Zinc occurs in the environment mainly in the +2 oxidation state (Lindsey 1979). Adsorption is the dominant fate of zinc, resulting in enrichment of zinc in suspended and bed sediments (Callahan et al. 1979). The mobility of zinc in soil has been characterized (Baes and Sharp 1983; Bergkvist et al. 1989; EPA 1980d; Hermann and Neumann-Mahlkau 1985; Kalbasi et al. 1978; Saeed and Fox 1977; Tyler and McBride 1982). No estimate for the atmospheric lifetime of zinc is available. Development of pertinent data on the atmospheric processes important for zinc speciation in the atmosphere would be helpful. Development of this information would permit construction of a comprehensive model for the transport and interaction of zinc not only in air but in other media as well. Transformation in air and water can occur as a result of changes in chemical speciation (Anderson et al. 1988; Callahan et al. 1979; EPA 1980d; Stokinger 1981). Data that describe the transformation processes for zinc in soil or the fate of zinc in soil are needed. A model of zinc flux from all environmental compartments would be useful for providing information on the overall environmental fate of zinc.

Bioavailability. Zinc can be absorbed following inhalation (Drinker and Drinker 1928; Hamdi 1969), ingestion (Aamodt et al. 1983; Davies 1980; Johnson et al. 1988; Methfessel and Spencer 1973; NAWNRC 1979; Spencer et al. 1985) or dermal contact (Agren 1990; Gordon et al. 1981; Hallmans 1977; Keen and Hurley 1977). No estimates of the bioavailability of zinc after inhalation of zinc particles in air, ingestion from water and soil, or skin contact with bath water or soil were located. The bioavailability of zinc is higher in media with a low pH, as a result of increased zinc solubility and ionization. If zinc is partly present in an irreversibly adsorbed state in soil, this part is not available for skin absorption. It would be useful to develop quantitative data on the bioavailability of zinc from various environmental media.

Food Chain Bioaccumulation. Zinc bioconcentrates moderately in aquatic organisms, and this bioconcentration is higher in crustaceans and bivalve species than in fish (EPA 1987~; Ramelow et al. 1989). Zinc does not concentrate in plants, and it does not biomagnify through the terrestrial food chain (Biddinger and Gloss 1984; Callahan et al. 1979; Hegstrom and West 1989; Levine et al. 1989).

Exposure Levels in Environmental Media. Zinc has been detected in air (Barrie and Hoff 1985; Duce et al. 1975; EPA 1980d; Evans et al. 1984; John et al. 1973; Lioy et al. 1978; Lloyd and Showak 1984; Patterson et al. 1977; Ragaini et al. 1977; Saltzman et al. 1985; Zoller et al. 1974) water (Coale and Flegal 1989; Cole et al. 1984; EPA 1980d; Hale 1977; HAZDAT 1993; Maessen et al. 1985; Minear et al. 1981; NAS 1977; Ohanian 1986; Schock and Neff 1988; Shiller and Boyle 1985; Windom et al. 1991), soil (Beavington 1975; Connor and Shacklette 1975; EPA 1980d; Haines 1984; HAZDAT 1993; Johnson et al. 1990; Mayer and Manning 1990; Mumma et al. 1984, 1990, 1991; Schalscha et al. 1982), and food (Coleman et al. 1992; Gartrell et al. 1986a; Mahaffey et al. 1975; Weigert 1991). However, since most of the data are not current, i.e., within the last 3 years, additional data would be useful to provide a more complete characterization of human exposure and the trend in zinc concentrations in various environmental media. Estimates have been made for human intake of zinc from food and drinking water (EPA 1980d; Gartrell et al. 1986a; NAS 1977; NAS/NRC 1989b; Pennington et al. 1986; Sharrett et al. 1982a, 1982b). Further data are needed on estimated daily intakes from inhalation resulting from occupational exposures.

Reliable monitoring data for the levels of zinc in contaminated media at hazardous waste sites are needed so that the information obtained on levels of zinc in the environment can be used in combination with the known body burden of zinc to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Zinc has been detected in fingernails, toenails, hair, all tissues, organs, skull and skeletal muscle, blood, feces, urine, sweat, and saliva (Greger and Sickles 1979; Hambidge et al. 1972; Henkin et al. 1975a; Llobet et al. 1988a; NASNRC 1979; Prasad et al. 1963a; Prevost et al. 1985; Saltzman et al. 1990; Schroeder et al. 1967; Takagi et al. 1988; Wastney et al. 1986; Wilhelm et al. 1991). Most of the data on occupational exposure levels of zinc are outdated (NIOSH 1976, 1984b). Additional information on potentially exposed workers

and exposure levels would provide a more accurate characterization of occupational exposures in the United States. Current biological monitoring data on zinc are needed for populations surrounding hazardous waste sites.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for zinc were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 On-going Studies

No long-term research studies were located regarding the environmental fate of zinc. However, remedial investigations and feasibility studies on the NPL sites known to have zinc contamination are expected to be completed in the near future and may add to the current knowledge regarding the transport and transformation of zinc in the environment. In addition, environmental monitoring currently being conducted at NPL hazardous waste sites will likely add to the current database on environmental levels of zinc.

No long-term research projects or other on-going studies were located regarding occupational or general population exposures.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting,' and/or measuring, and/or monitoring zinc, its metabolites, and other biomarkers of exposure and effect to zinc. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

Zinc is ubiquitous in both the environment and the laboratory. Since many biological and environmental samples contain low levels of zinc, it is easy to contaminate the samples. While analyzing samples, it is imperative that special precautions be taken to avoid sample contamination in order to obtain accurate results and ensure the integrity of the sample. Blood collection tubes are potential sources of zinc contamination (Delves 1981). An example of failure to institute proper measures to control sample contamination, which led to inaccuracies in reported data, was described by Windom et al. (1991). Methods that can be used to avoid reporting erroneous results include interlaboratory data comparison (Galloway et al. 1983) or use of standard reference materials, such as certified SRM 1549 (nonfat powdered milk) available from the National Institute of Standards and Technology (Perry 1990).

6.1 BIOLOGICAL MATERIALS

Table 6-l lists the applicable analytical methods used for determining zinc in biological fluids and tissues.

Atomic absorption spectrometry (AAS) using a furnace atomizer is a common and simple laboratory technique. It has become the method of choice for zinc analysis in biological samples including bone, liver, hair, blood, and urine. It is an economical method for determining trace

TABLE 6-1. Analytical Methods for Determining Zinc in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Breath	Personal sampler cartridges	ICP; AES	0.6 μg/L	94–101	NIOSH 1984a (method 7300)
		AAS, flame	3 μg/sample	NR	NIOSH 1984a (method 7030)
Blood or tissue	Acid digestion with $HNO_3/HClO_4$, H_2SO_4, measure at 213.9 nm	ICP; AES	1 μg/100 g (blood); 0.2 μg/g (tissue)	103	NIOSH 1984a (method 8005)
Urine	Acid digestion of oxygen plasma ashing; extract with polydithiocarbamate resin; measure at 213.9 nm	ICP; AES	0.1 μg/sample	100	NIOSH 1984a (method 8310)
Semen	Microwave wet acid digestion	GFAAS	400 μg/L	96–104	Alvarado et al. 1991
Fingernails	Digest nail samples with concentrated nitric acid; heat at 65°C for 1 hour; cool and dilute with deionized water	AAS, graphite furnace	NR	NR	Sohler et al. 1976

TABLE 6-1. Analytical Methods for Determining Zinc in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liver	Acid digestion with mixtures of different acids; distill volatile elements	Radiochemical NAA	NR	98	Lievens et al. 1977
Liver	Homogenize sample with water; add HCl; shake; centrifuge; dilute	FAAS	40 µg/L	100	Luterotti et al. 1992
Muscle tissue	Mineralize sample in muffle furnace; dissolve in HNO_3	FIA	3 µg/L	NR	Fernandez et al. 1992b
Blood	Separate serum from blood by centrifugation; transfer a portion of serum into an ampule of highly pure silica and dry; irradiate capsules at a thermal neutron density of $5x0^3 n/cm^{-2}/second^{-1}$	Instrumental NAA	0.0005 µg/L	>100	Jurgensen and Behne 1977
	Feed radiotracer ^{65}zinc; measure zinc activity in blood at 14 days	Tracer technique	NR	88	Watson et al. 1987

TABLE 6-1. Analytical Methods for Determining Zinc in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood serum and red blood cells	Feed ^{68}zinc and ^{70}zinc and measure blood levels in a 24-hour sample and a sample taken immediately after zinc administration; wet ash sample; add APDC precipitant; dissolve precipitate in HNO_3; irradiate	Isotope tracer technique	NR	NR	Janghorbani et al. 1981
Blood	Feed $^{65}ZnCl_2$ orally; measure zinc blood levels and whole blood count	Radiotracer technique — whole blood count and blood level measurement	NR	88	Watson et al. 1987
Bloodstain	Place drop of blood on filter paper; cut away excess paper; optional dry ash; add HCl; shake	AAS	NR	NR	Fan et al. 1991
Thoracic aorta, lung, myocardium, spleen	Homogenize sample; complete wet ashing with HNO_3	AAS	NR	NR	Marks et al. 1972

TABLE 6-1. Analytical Methods for Determining Zinc in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Feces	Give ^{67}Zn through diet; treat fecal samples with H_2O_2; prepare chelates	Isotope tracer technique	NR	>95 (^{67}Zn); 71 (^{70}Zn)	Johnson 1982
Feces	Feed ^{70}Zn, ^{68}Zn, and ^{64}Zn orally; homogenize sample; evaporate; ash; HNO_3 digestion; boil; evaporate; add HCl; transfer to anion exchange column; prepare eluate; irradiate	Isotope tracer technique, NAA	NR	NR	Ni et al. 1991
Bone	Acid digestion of dried bone ash with concentrated HNO_3; evaporate to dryness and add more concentrated HNO_3; remove silica residue by filtration; transfer samples to polyethylene bottles	AAS	NR	NR	Szpunar et al. 1978

TABLE 6-1. Analytical Methods for Determining Zinc in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Hair	Digest clean sample in acid mixture	AAS	20 μg/g	NR	Wilhelm et al. 1991
Hair	Rinse sample with hexane; wet or dry ash with HNO_3	EDXRF	0.001 μg/L	NR	Folin et al. 1991
Hair	Rinse sample with hexane; wet or dry ash with HNO_3	AAS	0.001 μg/L	NR	Folin et al. 1991
Hair	Digest clean sample in acid mixture	ICP-AAS	NR	81–102	Takagi et al. 1988
Serum and plasma	Separate serum and plasma by centrifugation; keep stored in glass tubes at -20°C until analysis; thaw to room temperature prior to analysis	AAS	NR	NR	Shaw et al. 1982
Milk	Ash; lyophilize; wet-ash with HNO_3; add H_2O_2; dry; dissolve in HCl and NH_4Cl; extract with DDDC	ICP-MS	0.06 μg/sample	NR	Patterson et al. 1992

TABLE 6-1. Analytical Methods for Determining Zinc in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Milk	Dilute sample with Triton X-100	AAS, electrothermal	0.052 μmol/L	86–106	Arnaud et al. 1991
Saliva	Lashley cup placed over one of the Stenson's ducts; secretion stimulated with lemon candies; discard first 5–10 mL; collect ≈120 mL	AAS	NR	NR	Langmyhr et al. 1979

AAS = atomic absorption spectroscopy; AES = atomic emission spectroscopy; APDC = ammonium pyrolidine dithiocarbamate; DDDC = diethylammonium diethyldithiocarbamate; EDXRF = energy dispersive x-ray fluorescence; FAAS = flame atomic absorption spectroscopy; FIA = flow injection analysis; GFAAS = graphite furnace atomic absorption spectroscopy; HCl = hydrogen chloride; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; H_2O_2 = hydrogen peroxide; H_2SO_4 = sulfuric acid; ICP = inductively coupled argon plasma spectroscopy; MS = mass spectrometry; NAA = neutron activation analysis; NH_4Cl = ammonium chloride; NR = not reported; Zn = zinc; $ZnCl_2$ = zinc chloride

element composition with good precision, although its sensitivity is not always good (high ppm levels). Its principal limitation is that it requires analyzing each element separately (Szpunar et al. 1978). Graphite furnace AAS (GFAAS) has been used to determine zinc in human semen. Recovery (96-104%) was good, and preparation by microwave wet acid dissolution was more accurate than the standard water dilution method (Alvarado et al. 1991). AAS has also been used to determine zinc in bloodstains on filter paper. This method is accurate, reproducible, and acceptable for routine clinical testing using both dry ashing and direct extraction sample preparation (Fan et al. 1991). Electrothermal AAS is more sensitive than flame AAS (FAAS) and has been used to determine very low levels of zinc (detection limit, 0.052 μmol/L) in human milk (Arnaud et al. 1991). Zinc concentrations in liver have been accurately quantified by FAAS. Homogenization of tissue samples coupled with FAAS resulted in 100% recoveries, accuracies of 0-3%, and a detection limit of 0.04 mg/L (Luterotti et al. 1992).

Multi-elemental analysis has been used to detect zinc and other trace metals in biological fluids and tissues. For determination of metallic constituents in biological samples, such as liver, samples were digested with mixtures of different acids, volatile elements were distilled by selective distillation, and a cleanup step was performed using ion exchange chromatography prior to assay by neutron activation analysis (NAA) (Lievens et al. 1977). Recovery (98%) and precision (< 10% coefficient of variation [CV]) were excellent. Although the limit of detection for zinc was not reported, based on the reported results this method can detect levels ranging from the low- to the sub-ppm range (Lievens et al. 1977). The NAA technique has also been used to detect zinc in urine and blood samples. Jurgensen and Behne (1977) used the technique to measure human serum levels of trace elements including zinc. Recovery and precision for this method are very good. Sensitivity was not reported.

Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) is used for multi-element determinations in blood and tissue samples. Detection in urine samples requires extraction of the metals with a polydithiocarbamate resin prior to digestion and analysis (NIOSH 1984a). Other satisfactory analytical methods include direct current plasma emission spectroscopy and determination by AAS, and inductively coupled argon plasma spectroscopy-mass spectrometry (ICP-MS) (Patterson et al. 1992; Shaw et al. 1982). Flow injection analysis (FIA) has been used to determine very low levels of zinc in muscle tissue. This method provides very high sensitivity,

low detection limits (3 ng/mL), good precision, and high selectivity at trace levels (Fernandez et al. 1992b).

The use of stable isotopes or tracers to study zinc absorption in humans with subsequent analysis by mass spectrometry has been reported in the literature. Analysis of fecal samples obtained 3 and 6 days after the administration of zinc-65 isotope in food showed that between 45% and 75% of zinc isotope was absorbed (Johnson 1982). The results indicated satisfactory detection of the zinc-67 isotope in human feces, while the zinc-70 isotope was not as detectable. Better precision and recovery were obtained for the zinc-67 isotope (2.4% CV; >95% recovery) than for the zinc-70 isotope (38% CV; 71% recovery). Sample detection limits were not reported. Total reported sample preparation time was <2 hours, and it took only 5-10 minutes to analyze each sample on the mass spectrometer.

A practical method, based on NAA, was developed for accurate measurement of the stable isotopes zinc-68 and zinc-70 in human plasma and red blood cells (Janghorbani et al. 1981). This method can provide an alternative to the use of radiolabeled zinc. It is more complex and time consuming than those used to measure radiolabeled zinc levels. As with any isotopic method, isotope exchange may invalidate calculation of net absorption, but this potential problem was not investigated. Precision was very good (<10%). Sensitivity and accuracy were not reported.

Radionuclide studies offer an additional method to investigate the factors that affect trace element absorption. Radioactivity emitted by the radionuclide was measured in blood 14 days after the oral ingestion of zinc-65 and compared with the amount of radioactivity emission determined by whole-body counting (Watson et al. 1987). The results indicated that, where whole-body counting facilities were not available, measurement of radioactivity emitted in blood was a reasonable alternative for the prediction of zinc absorption. Recovery for this method was adequate (88%); precision was acceptable (<17% CV). The limit of detection for zinc was not reported.

6.2 ENVIRONMENTAL SAMPLES

Table 6-2 lists the methods used for analyzing zinc in environmental samples.

TABLE 6-2. Analytical Methods for Determining Zinc in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect air particulates on teflon filters; digest with HNO_3	NAA (nondestructive)	NR	NR	Zoller et al. 1974
Atmospheric aerosols	Collect sample on cellulose filter; digest with HNO_3; filter; dry; add HNO_3; adjust pH; add KNO_3	ASV	13.7 µg/L	NR	Casassas et al. 1991
Water and waste water	Acid digestion	AAS, direct aspiration	5 µg/L	99.3–111 at 60–310 µg/L	EPA 1979c (method 289.1)
Water and waste water		AAS, furnace technique	0.05 µg/L	NR	EPA 1979c (method 289.2)
Water	HNO_3 digestion; read samples at 213.9 nm	AAS, flame technique	NR	NR	AOAC 1984 (method 33.089)
Water	Mineralize sample in muffle furnace; dissolve in HNO_3	FIA	3 µg/L	NR	Fernandez et al. 1992b
Seawater	APDC-MIBK extraction	AAS	0.05 ppb	NR	Brooks et al. 1967

TABLE 6-2. Analytical Methods for Determining Zinc in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Seawater	Take a sample digest in the electrochemical cell; adjust pH; add chelating agent and aerate	Cathodic stripping voltammetry	$7x0^{-11}$ M	NR	van den Berg 1986
Crude oil	Digest sample with HNO_3; extract with MIBK or dilute with MIBK	AAS	0.8 μg/g	NR	Elson et al. 1981
Soil, solid waste, sludges	Acid digestion	ICP or flame AAS	2 μg/L (in solution)	102.5 at 80 μg/L	EPA 1986a (methods 6010 and 3050)
Soil, solid waste, sludges		AAS, direct aspiration0.005 μg/L (in solution)NREPA 1986a (method 7950)			
Soil	Extract with DTPA and NH_4HCO_3-DTPA	ICP	NR	NR	Boon and Soltanpour 1991
Plants	Digest samples with acids	AAS	NR	NR	AOAC 1984 (method 3.013)

TABLE 6-2. Analytical Methods for Determining Zinc in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plants	Digest samples with acid; extract with dithiozone reagent and CCl_4; add HCl and CCl_4; read at 525 nm for mixed-color method and at 535 nm for single-color method	Mixed and single color methods — spectrophotometric analysis	NR	NR	AOAC 1984 (methods 3.054 and 3.061)
Food	Digest sample with acid mixtures; remove sulfide, nickel, and cobalt; add dithiozone and CCl_4; measure transmission at 540 nm	Colorimetric method	NR	NR	AOAC 1984 (method 25.168)
Food	Digest samples with acid mixtures	AAS	NR	NR	AOAC 1984 (method 25.175)
Food	Dry ash sample in muffle oven; dilute with HNO_3	FAAS; FES	0.24 μg/g	97–100	Morales-Rubio et al. 1992

TABLE 6-2. Analytical Methods for Determining Zinc in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Clarify; de-gas; dilute with deionized water; add HNO_3 to solid samples	GFAAS	NR	90–113	Wagner et al. 1991
Food	Sample dependent; blend; lipophilize; grind; oven-dry; press into pellets	EDXRF	0.8 ppm	NR	Nielson et al. 1991
Shellfish	HNO_3 digestion in microwave; dilute with deionized water	FAAS	0.12 ppm	80	McCarthy and Ellis 1991
Natural waters	Acid digestion	AAS	0.005 ppm	NR	Fishman 1966

AAS = atomic absorption spectroscopy; APDC = ammonium pyrolidine dithiocarbamate; ASV = anodic stripping voltammetry; CCl_4 = carbon tetrachloride; DTPA = diethylenetriaminepentaacetic acid; EDXRF = energy dispersive x-ray fluorescence; FAAS = flame atomic absorption spectrometry; FES = flame emission spectrophotometry; FIA = flow-injection analysis; HCl = hydrochloric acid; $HN0_3$ = nitric acid; ICP = inductively coupled argon plasma spectroscopy; KNO_3 = potassium nitrite; MIBK = methyl isobutyl ketone; NAA = neutron activation analysis; NH_4HCO_3-DTPA = ammonium bicarbonate–diethylenetriaminepentaacetic acid; NR = not reported

6. ANALYTICAL METHODS

Variations of the AAS technique are commonly used to detect zinc levels in air, water, and soil samples, as well as in certain plant and food samples. Inductively coupled argon plasma spectroscopy (ICP) is a recommended test method for analyzing solid waste samples to measure zinc. Using either the ICP method or the AAS method, operators of hazardous waste management facilities can determine whether a given sample is hazardous, based on the level of zinc in a sample of solid waste leachate.

AAS has been used to determine zinc concentrations in natural waters (Fishman 1966). AAS is a rapid method of measuring zinc, with the detection limit (0.005 ppm) being somewhat better than those obtained using other methods. Recovery and precision data were not reported. A year later, Brooks et al. (1967) demonstrated a simple extraction system consisting of only two reagents, ammonium pyrollidine dithiocarbamate (APDC) and methyl isobutylketone (MIBK), with subsequent analysis by AAS to measure particulate and "soluble" zinc in seawater. Sensitivity was in the sub-ppm range, and precision was good (3% CV). Accuracy was not reported.

FAAS, coupled with microwave digestion and GFAAS, has been used to determine the concentration of zinc in food and shellfish samples. Limits of detection ranged from 0.12 to 0.24 ppm, with recoveries ranging from 80% to 113%. Precision and recovery using microwave digestion were comparable to traditional wet ashing and superior to dry ashing in shellfish samples (AOAC 1984; McCarthy and Ellis 1991; Morales-Rubio et al. 1992). GFAAS was also used to determine low levels of zinc in beer. Recovery (94-106%) and precision (4.2% CV) were excellent. Sensitivity was not reported (Wagner et al. 1991). Energy dispersive x-ray tluorescence (EDXRF) for multielement analysis has been used to detect zinc in dried food samples with better precision (and a detection limit of 0.8 ppm) than AAS methods (Nielson et al. 1991).

Cathodic stripping voltammetry, also known as adsorption voltammetry, has been used to detect various metal ions in a 10^{-l0} to 10^{-10} M range in seawater (van den Berg 1986). APDC was used as a chelating agent for zinc. Because of the great sensitivity and specificity of APDC for zinc, it can be detected directly in the unaltered sample. Recovery and precision data were not reported. Similarly, differential pulse cathodic stripping voltammetry (DPCSV) and differential pulse anodic stripping voltammetry (DPASV) after complexation with APDC have been used for determining zinc speciation at nanomolar concentrations in ocean waters (Donat and Bruland 1990). Recovery and precision data were not reported. Anodic stripping voltammetry (ASV) has been

used to detect zinc and other metal ions simultaneously at trace levels in atmospheric aerosols. This method is primarily used for small samples with very low concentrations of zinc. The limit of detection was 13.7 ng/L, and the recovery was not reported (Casassas et al. 1991).

AAS has been used to measure heavy metals, including zinc, in various oil samples collected at different stages of oil refining (Elson et al. 1981). These samples were prepared using three techniques (digestion, extraction, and dilution) prior to AAS analysis; recovery from crude oil was higher with wet digestion. Sensitivity for zinc was in the low-ppm range. Accuracy and precision were not reported.

An ion chromatographic method has been proposed for simultaneous determination of several elements including zinc in soil (Basta and Tabatabai 1990). In this method, after preliminary sample treatment, the metals are separated by ion chromatography, and the separated elements are quantitated by ultraviolet-visible detection of zinc-PAR (4-[2-pyridylazo] resorcinol) colored complexes. The limit of detection for zinc by this method is 5 ppb in soil extract. Precision was ≤2.5% CV. Accuracy was not reported. The concentration of zinc in soil was determined by ICP coupled with an ammonium bicarbonate-diethylenetriaminepentaacetic acid (NH_4,HCO_3,-DTPA) extraction procedure. (This method is superior to AAS and calorimetric methods because of the capacity for multielemental analysis.) This method can be used to screen soils for zinc. Limits of detection and recovery were not reported (Boon and Soltanpour 1991).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of zinc is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of zinc.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be

interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. AAS is the most commonly used analytical method to determine zinc levels in plasma, bone, fingernails, hair, and other biological tissues and body fluids (Alvarado et al. 1991; Arnaud et al. 1991; Fan et al. 1991; Langmyhr et al. 1979; Luterotti et al. 1992; Marks et al. 1972; NIOSH 1984a; Shaw et al. 1982; Sohler et al. 1976; Szpunar et al. 1978; Wilhelm et al. 1991). This method generally is sensitive enough to measure background levels in the population and levels at which biological effects occur. The method is specific and precision is good. However, improved sensitivity and recovery data are needed in order to better evaluate the relationship between body and environmental exposure levels of zinc. Other methods that are specific for measuring zinc in biological fluids and tissues include NAA, ICP-AES, FIA, and isotope tracers techniques (Fernandez et al. 1992b; Janghorbani et al. 1981; Johnson 1982; Lievens et al. 1977; NIOSH 1984a; Watson et al. 1987). Sensitivity and/or recovery data for these methods are needed to more fully evaluate the reliability of these methods as predictors of environmental exposure.

Although several biomarkers for the effects of zinc have been identified (increased levels of serum amylases and lipase, non-iron responsive anemia, and decreased HDL cholesterol levels), these biomarkers of effect are not specific for zinc (Cotran et al. 1989; Suber 1989). Standard laboratory tests are available that can measure these biomarkers (Henry 1984). These methods are sensitive, accurate, and reliable enough to measure background levels in the population and levels at which biological effects occur. The development of methods for determining biomarkers of effect specific for zinc would be beneficial in assessing whether an individual has been exposed to zinc.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods of adequate sensitivity and specificity are available for determining levels of zinc in environmental media (AOAC 1984; Basta and Tabatabai 1990; Brooks et al. 1967; Casassas et al. 1991; Donat and Bruland 1990; Elson et al. 1981; EPA 19795 1986a; Fishman 1966; McCarthy

and Ellis 1991; Morales-Rubio et al. 1992: Nielson et al. 1991; van den Berg 1986; Wagner et al. 1991; Zoller et al. 1974). Some of these methods are precise and sensitive enough to measure background levels in the environment and levels at which health effects occur. These methods can distinguish between soluble zinc, insoluble zinc, and chelated zinc in water (Donat and Bruland 1990). Studies to obtain more information on the accuracy of these methods as well as improved sensitivity are needed to better assess the risk of exposure for these media. Research investigating the relationship between levels measured in air, water, and soil and observed health effects would increase our confidence in existing methods and/or indicate where improvements are needed.

6.3.2 On-going Studies

No on-going studies were located regarding techniques for measuring or detecting zinc in biological fluids, tissues, or environmental samples.

7. REGULATIONS AND ADVISORIES

Zinc (fume and dust) and its compounds are on the list of chemicals appearing in “Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986” (EPA 1991d).

The national and state regulations and guidelines pertaining to zinc and compounds in air, water, and food are summarized in Table 7-l. No international regulations or guidelines applicable to zinc or its compounds were found.

ATSDR has derived an intermediate oral MRL for zinc based on hematological effects, specifically decreased hematocrit, serum ferritin, and erythrocyte superoxide dismutase activity, in women given supplements containing zinc gluconate for 10 weeks (Yadrick et al. 1989). The intermediate oral MRL has been adopted as the chronic oral MRL.

EPA has derived oral reference doses (RfDs) of 0.3 mg/kg/day for zinc, 0.05 mg/kg/day for zinc cyanide, and 0.0003 mg/kg/day for zinc phosphide (IRIS 1993). EPA has not derived an inhalation reference concentration (RfC) for zinc.

TABLE 7-1. Regulations and Guidelines Applicable to Zinc

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL		OSHA 1992 (29 CFR 1910.1000)
	Zinc chloride (fume)		
	TWA	1 mg/m^3	
	STEL (15-minute)	2 mg/m^3	
	Zinc chromate (as chromate)		
	Ceiling	0.1 mg/m^3	
	Zinc oxide		
	TWA (fume or respirable fraction)	5 mg/m^3	
	TWA (total dust)	10 mg/m^3	
	STEL (15-minute) (fume)	10 mg/m^3	
b. Water:			
EPA	Designated as a hazardous substance under the Federal Water Pollution Control Act	Yes	EPA 1989a (40 CFR 116.4)
	Designated as a toxic pollutant under the Clean Water Act	Yes	EPA 1981 (40 CFR 401.15)
EPA ODW	Secondary mazimum contaminant level for public water systems		EPA 1991b (40 CFR 143)
	Zinc	5 mg/L	
EPA OWRS	General pretreatment regulations		EPA 1988a
	Listed as a toxic pollutant	Yes	(40 CFR 403, Appendix B)
FDA	Permissible level in bottled water		FDA 1989
	Zinc	5.0 mg/L	(21 CFR 103.35)
c. Food:			
EPA	Tolerance for residues of fungicide basic zinc sulfate, calculated as elemental zinc, in or on raw agricultural commodities		EPA 1973 (40 CFR 180.244)
	Peaches	30 ppm	
d. Other:			
EPA OERR	Reportable quantity		EPA 1989b (40 CFR 302.4)
	Zinc[a]	1,000 pounds	
	Zinc acetate	1,000 pounds	
	Zinc ammonium chloride	1,000 pounds	
	Zinc borate	1,000 pounds	
	Zinc bromide	1,000 pounds	
	Zinc carbonate	1,000 pounds	
	Zinc chloride	1,000 pounds	
	Zinc cyanide	10 pounds	
	Zinc fluoride	1,000 pounds	
	Zinc formate	1,000 pounds	
	Zinc hydrosulfite	1,000 pounds	
	Zinc nitrate	1,000 pounds	
	Zinc phenosulfonate	5,000 pounds	

TABLE 7-1. Regulations and Guidelines Applicable to Zinc *(continued)*

Agency	Description	Information	References
NATIONAL (cont.)			
	Zinc phosphide	100 pounds	
	Zinc silicofluoride	5,000 pounds	
	Zinc sulfate	1,000 pounds	
	zinc, dichloro (4,4-dimethyl-5((((methylamino)carbonyl) oxy)limino)pentanenitrile)-, (T-4) (statutory)	1 pound	EPA 1990b (40 CFR 355, Appendix A)
	Extremely hazardous substances		EPA 1990b (40 CFR 355, Appendix A)
	Threshold planning quantity		
	Zinc, dichloro (4,4-dimethyl-5((((methylamino)carbonyl) oxy)limino)pentanenitrile)-, (T-4) (statutory)	100/10,000 pounds	
	Zinc phosphide	500 pounds	
EPA OSW	Dicarded commercial chemical products, off-specification species, container residues, and spill residues thereof		
	Listing as actue hazardous waste		EPA 1980a (40 CFR 261.33[e])
	Zinc cyanide	Yes	
	Zinc phosphide, when present at concentrations >10%	Yes[b]	
	Listing as toxic waste		EPA 1984a (40 CFR 261.33[f])
	Zinc phosphide, when present at concentrations ≤10%	Yes	
	Listing as a hazardous waste constituent		EPA 1991a (40 CFR 261, Appendix VIII)
	Zinc cyanide	Yes	
	Zinc phosphide	Yes	
EPA OTS	Toxic chemical release reporting		EPA 1991d (40 CFR 372)
	Zinc (fume or dust)	Yes	
Guidelines:			
a. Air:			
ACGIH	TLV		ACGIH 1991
	Zinc chloride (fume)		
	TWA	1 mg/m^3	
	STEL	2 mg/m^3	
	Zinc oxide		
	TWA (fume)	5 mg/m^3	
	TWA (total dust)	10 mg/m^3	
	STEL (fume)	10 mg/m^3	

TABLE 7-1. Regulations and Guidelines Applicable to Zinc *(continued)*

Agency	Description	Information	References
NATIONAL (cont.)			
NIOSH	REL		NIOSH 1992
	Zinc oxide (fume)		
	TWA	5 mg/m^3	
	STEL	10 mg/m^3	
	Zinc oxide (dust)		
	TWA	5 mg/m^3	
	TWA ceiling (15-minute)	15 mg/m^3	
	Zinc chloride (fume)		
	TWA	1 mg/m^3	
	STEL	2 mg/m^3	
b. Water:			
EPA OWRS	Ambient water quality criterion	5 mg Zn/L	EPA 1980c
NAS	Drinking water standard	5 mg Zn/L	NAS 1977
c. Food:			
NAS	RDA	15 mg/day (men) 12 mg/day (women)	NAS/NRC 1989b
d. Other:			
EPA	Oral RfD		
	Zinc	0.3 mg/kg/day	IRIS 1993
	Zinc cyanide	0.05 mg/kg/day	
	Zinc phosphide	0.0003 mg/kg/day	
STATE			
Regulations and Guidelines:			
a. Air:	Average acceptable ambient air concentrations		NATICH 1993
	Zinc		
Maryland		0.00	
Maine		0.00	
Montana	(24 hour)	39.3 µg/m^3	
Montana	(1 year)	6.55 µg/m^3	
New York	(1 year)	0.03 µg/m^3	
Vermont	(24 hour)	12.0 µg/m^3	
	Zinc chloride (fume)		
Arizona	(1 hour)	17.0 µg/m^3	
Arizona	(24 hour)	8.0 µg/m^3	
California (Mont.)		0.00	
Connecticut	(8 hour)	20.0 µg/m^3	
Florida (Tampa)	(8 hour)	0.01 µg/m^3	

TABLE 7-1. Regulations and Guidelines Applicable to Zinc *(continued)*

Agency	Description	Information	References
STATE (cont.)			
Florida (Fort Lauderdale)	(8 hour)	0.01 $\mu g/m^3$	
Florida (Pinella)	(8 hour)	10.0 $\mu g/m^3$	
Florida (Pinella)	(24 hour)	2.4 $\mu g/m^3$	
Maryland		0.00	
North Dakota	(8 hour)	0.01 $\mu g/m^3$	
North Dakota	(1 hour)	0.02 $\mu g/m^3$	
Nevada	(8 hour)	0.024 $\mu g/m^3$	
New York	(1 year)	3.3 $\mu g/m^3$	
Oklahoma	(24 hour)	20.0 $\mu g/m^3$	
South Dakota	(8 hour)	10.0 $\mu g/m^3$	
Texas	(30 min)	10.0 $\mu g/m^3$	
Texas	(1 year)	1.0 $\mu g/m^3$	
Virginia	(24 hour)	17.0 $\mu g/m^3$	
Vermont	(24 hour)	2.4 $\mu g/m^3$	
Washington (Southwest)	(24 hour)	3.3 $\mu g/m^3$	
	Zinc oxide (fume)		
Arizona	(1 hour)	83.0 $\mu g/m^3$	
Arizona	(24 hour)	40.0 $\mu g/m^3$	
Connecticut	(8 hour)	100.0 $\mu g/m^3$	
Florida (Tampa)	(8 hour)	0.05 $\mu g/m^3$	
Florida (Fort Lauderdale)	(8 hour)	0.05 $\mu g/m^3$	
Florida (Pinella)	(8 hour)	50.0 $\mu g/m^3$	
Florida (Pinella)	(24 hour)	12.0 $\mu g/m^3$	
Louisiana	(8 hour)	119.0 $\mu g/m^3$	
North Dakota	(8 hour)	0.05 $\mu g/m^3$	
North Dakota	(1 hour)	0.1 $\mu g/m^3$	
Nevada	(8 hour)	0.119 $\mu g/m^3$	
New York	(1 year)	16.7 $\mu g/m^3$	
Oklahoma	(24 hour)	500.0 $\mu g/m^3$	
Texas	(30 min)	50.0 $\mu g/m^3$	
Texas	(1 year)	5.0 $\mu g/m^3$	
Virginia	(24 hour)	83.0 $\mu g/m^3$	
Virginia	(24 hour)	170.0 $\mu g/m^3$	
Washington (Southwest)	(24 hour)	16.7 $\mu g/m^3$	

TABLE 7-1. Regulations and Guidelines Applicable to Zinc *(continued)*

Agency	Description	Information	References
STATE (cont.)			
	Drinking water quality		
Alabama		5 mg/L	CELDS 1993
Arizona		5 mg/L	FSTRAC 1990
California		5 mg/L	CELDS 1993
Colorado		5 mg/L	CELDS 1993
Delaware		5 mg/L	CELDS 1993
Florida		5 mg/L	CELDS 1993
Georgia		5 mg/L	CELDS 1993
Idaho		5 mg/L	CELDS 1993
Illinois		5 mg/L	CELDS 1993
Kansas		5 mg/L	FSTRAC 1990
Kentucky		5 mg/L	CELDS 1993
Louisiana		5 mg/L	CELDS 1993
Maine		5 mg/L	CELDS 1993
Minnesota	Classes A and B	5 mg/L	CELDS 1993
Missouri		5 mg/L	CELDS 1993
Nevada		5 mg/L	CELDS 1993
New Hampshire		5 mg/L	CELDS 1993
New Jersey		5 mg/L	CELDS 1993
New York		5 mg/L	CELDS 1993
Oregon		5 mg/L	CELDS 1993
Rhode Island		5 mg/L	FSTRAC 1990
Tennessee		5 mg/L	CELDS 1993
Texas		5 mg/L	CELDS 1993
Utah		5 mg/L	CELDS 1993
Vermont		5 mg/L	FSTRAC 1990
Virginia		5 mg/L	CELDS 1993
Washington		5 mg/L	CELDS 1993
Wisconsin		5 mg/L	CELDS 1993
	Groundwater		CELDS 1993
Colorado	Agricultural standards	2 mg/L	
Massachusetts	MAL for Classes I and II	5 mg/L	
Missouri	Criteria	5 mg/L	
Nebraska	MCL	5 mg/L	
New Jersey	Criteria for Classes GW1, GW2, GW3	5 mg/L	
New Mexico	Domestic water supply	10 mg/L	
New York	MAC	5 mg/L	
North Carolina		5 mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Zinc *(continued)*

Agency	Description	Information	References
STATE (cont.)			
Oregon	Quality guidance levels	5 mg/L	
Virginia	Statewide standards	0.05 mg/L	
Wisconsin	Public welfare standards		
	Enforcement standard	5 mg/L	
	Preventive action limit	2.5 mg/L	
Wyoming	MCL		
	Class I (Domestic)	5 mg/L	
	Class II (Agriculture)	2 mg/L	
	Class II (Livestock)	25 mg/L	
	Surface water		CELDS 1993
California	Background seawater concentrations	8 µg/L	
	Estimate of chronic toxicity	51 µg/L	
District of Columbia	Total recoverable		
	Class C	0.05 mg/L	
	Class E	5 mg/L	
Florida	Quality standard	1 mg/L	
	Class III waters	0.03 mg/L	
Iowa	Maximum chemical level		
	Class B	1 mg/L	
	Class C	1 mg/L	
Maryland	Criteria for aquatic life protection		
	Freshwater acute	120 µg/L	
	Freshwater chronic	110 µg/L	
	Salt water acute	95 µg/L	
	Salt water chronic	86 µg/L	
Mississippi	Freshwater acute criteria	65 µg/L[c]	
	Freshwater chronic criteria	59 µg/L[c]	
	Salt water acute criteria	95 µg/L	
	Salt water chronic criteria	86 µg/L	
North Carolina	Action level	50 µg/L	
Oklahoma	Acute criteria	Must be calculated[d]	
	Chronic criteria	Must be calculated[e]	
Puerto Rico	Standards for toxic substances	50 µg/L	
Texas	Fresh acute and chronic	Must be calculated[d]	
	Marine acute	98 µg/L	
	Marine chronic	89 µg/L	
Virginia	Criteria for protection of aquatic life		
	Freshwater chronic	47 µg/L	
	Salt water chronic	58 µg/L	
Wyoming	Water quality standard		
	Special Class A	0.05-0.6mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Zinc *(continued)*

Agency	Description	Information	References
STATE (cont.)			
	Public water		CELDS 1993
Arkansas	MCC	5 mg/L	
Florida	Class I waters	0.03 mg/L	
Ohio	Secondary MCL	5 mg/L	
Oklahoma	Raw water numerical limits	5 mg/L	
Virginia	Surface water for human consumption	5 mg/L	
West Virginia	Secondary MCL	5 mg/L	
	General water quality standards		CELDS 1993
Alabama	Freshwater acute criteria	Must be calculated[d]	
	Freshwater chronic criteria	Must be calculated[e]	
	Marine acute criteria	96 µg/L	
	Marine chronic criteria	86 µg/L	
	Consumption of fish and water	5 mg/L	
	Consumption of fish only	5 mg/L	
Arizona	Water quality criteria		
	Domestic water source	5000 µg/L[f]	
	Full body contact	28000 µg/L	
	Partial body contact	28000 µg/L	
	Acute and chronic criteria for aquatic and wildlife uses		
	Cold water fishery, warm water fishery, effluent dominated water, and ephemerol	Dependent upon dissolved	
California	Limitations for protection of marine aquatic life		
	6-Month median	20 µg/L	
	Daily maximum	80 µg/L	
	Instantaneous maximum	200 µg/L	
Connecticut	Aquatic life criteria		
	Freshwater acute	35.3 µg/L	
	Freshwater chronic	12.3 µg/L	
	Salt water acute	95 µg/L	
	Salt water chronic	86 µg/L	
Delaware	Criteria for protection of aquatic life		
	Fresh acute	Must be calculated[d]	
	Fresh chronic	Must be calculated[e]	
	Marine acute	95 µg/L	
	Marine aquatic	86 µg/L	
Hawaii	Standards for all waters		
	Freshwater acute	22 µg/L[g]	
	Freshwater chronic	22 µg/L[g]	
	Salt water acute	95 µg/L	
	Salt water chronic	86 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Zinc *(continued)*

Agency	Description	Information	References
STATE (cont.)			
Illinois	Chemical constituent level	1 mg/L	
	Secondary contact and indigenous aquatic life		
	Chemical constituent levels	1 mg/L	
Indiana	Acute aquatic criteria	Must be calculated[d]	
	Chronic aquatic criteria	Must be calculated[e]	
Louisiana	Criteria for aquatic life protection		
	Acute		
	Freshwater	65, 120, 210 µg/L[h]	
	Marine water	95.00 µg/L	
	Chronic		
	Freshwater	59, 110, 190 µg/L[h]	
	Marine water	86.00 µg/L	
Mississippi	Criteria for all waters		
	Organisms only	5 mg/L	
	Water and organisms	5 mg/L	
Missouri	Protection of aquatic life		
	CWF chronic	175 µg/L	
	Lakes chronic	105 µg/L	
	GWWF chronic	245 µg/L	
	LWWF chronic	1065 µg/L	
	CWF acute	190 µg/L	
	Lakes acute	115 µg/L	
	GWWF acute	270 µg/L	
	LWWF acute	1180 µg/L	
	Human health protection		
	CWF chronic	240 µg/L	
	Lakes chronic	150 µg/L	
	GWWF chronic	345 µg/L	
	LWWF chronic	1505 µg/L	
	CWF acute	270 µg/L	
	Lakes acute	165 µg/L	
	GWWF acute	380 µg/L	
	LWWF acute	1660 µg/L	
	Drinking water supply		
	CWF chronic	310 µg/L	
	Lakes chronic	190 µg/L	
	GWWF chronic	440 µg/L	
	LWWF chronic	1920 µg/L	
	CWF acute	345 µg/L	
	Lakes acute	210 µg/L	
	GWWF acute	490 µg/L	
	LWWF acute	2120 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Zinc *(continued)*

Agency	Description	Information	References
STATE (cont.)			
Nevada	Irrigation	<2 mg/L	
	Watering of livestock	<25 mg/L	
	Propagation of wildlife only	<25 mg/L	
New York	MAC		
	Classes A, A-S, AA, AA-S, GA	300 µg/L[i]	
	Classes A, A-S, AA, AA-S, B, C	30 µg/L[j]	
	Class D	Must be calculated[k,l]	
	Classes SA, SB, SC	58 µg/L[j]	
	Class SD	170 µg/L[k]	
North Dakota	Class I streams	Must be calculated[d]	
Oklahoma	Maximum effluent concentration	1 mg/L	
South Dakota	Aquatic life value concentrations		
	Acute (CMC)	120.0 µg/L[h]	
	Chronic (CCC)	110.0 µg/L[h]	
Utah	Criteria for aquatic wildlife		
	3A, 3B, 3C, and 3D		
	1-hour average	120 µg/L	
	4-day average	110 µg/L	
	Protection of human health		
	Class 3 MCL	5000 µg/L	
Vermont	Criteria for protection of aquatic biota for all classes		
	Acute	Must be calculated[l]	
	Chronic	Must be calculated[d]	
West Virginia	Water quality criterion		
	B2	47 µg/L	
	B1, B3	Dependent on hardness	
	A	Dependent on hardness	

[a]No reporting of releases of this hazardous substance is required if the diameter of the pieces of the solid metal released is equal to or exceeds 100 micrometers (0.004 inches).
[b]The primary hazardous properties of this material are toxicity and reactivity.
[c]Hardness-dependent parameter. All criteria are as indicated at hardness less than or equal to 50 mg/L, as calcium carbonate. If hardness exceeds 50 mg/L, as calcium carbonate, then criteria is equal to result of hardness based equations as found in quality criteria for water.
[d]exp(0.8473[ln(hardness as mg/L)] + 0.8604) µg/L
[e]exp(0.8473[ln(hardness as mg/L)] + 0.7614) µg/L
[f]Total recoverable
[g]The value listed is the minimum standard. Depending upon the receiving water calcium carbonate hardness, higher standards may be calculated using the respective formula in the EPA publication "Quality Criteria for Water" (EPA 440/5-86-001, revised May 1, 1987).
[h]Hardness-dependent criteria for this chemical
[i]This standard is health based.
[j]This standard is aquatic based, and the procedure used as a basis for the standard is propagation.

(Footnotes continued on next page)

TABLE 7-1. Regulations and Guidelines Applicable to Zinc *(continued)*

Agency	Description	Information	References

FOOTNOTES (cont.)

[k]This standard is aquatic based, and the procedure used as a basis for the standard is survival.
[l]Calculated as exp(0.83[ln(hardness as mg/L)] + 1.95) µg/L

ACGIH = American Conference of Governmental Industrial Hygienists; Class I (Florida) = Surface waters (except mixing zones) designated as Class I for use as a potable supply; Class I (Massachusetts) = Fresh ground waters found in the saturated zone of unconsolidated deposits or consolidated rock and bed rock - a source of potable water supply; Class I (Wyoming) = Suitable for domestic use; Class I streams (North Dakota) = The quality of waters in this class shall be such as to permit the propagation or life, or both, of resident fish species and other aquatic biota and shall be suitable for boating, swimming, and other water recreation; Class II (Massachusetts) = Saline waters found in the saturated zone of the unconsolidated deposits or consolidated rock and bed rock as a source of potable mineral waters, for conversion to fresh potable waters, or as raw material for the manufacture of sodium chloride or its derivatives or similar products; Class II (Wyoming) = Suitable for agriculture where soil conditions and other factors are adequate; Class III (Florida) = Designated for recreation and propagation and maintenance of a healthy population of fish and wildlife; Class III (Wyoming) = Suitable for livestock; Class 3 (Utah) = Protected for in-stream use by aquatic wildlife; Class 3A (Utah) = Protected for cold water species of game fish and other cold water aquatic life, including the necessary aquatic organisms in their food chain; Class 3B (Utah) = Protected for warm water species of game fish and other warm water aquatic life, including the necessary aquatic organisms in their food chain; Class 3C (Utah) = Protected for nongame fish and other aquatic life, including the necessary aquatic ortanisms in their food chain; Class 3D (Utah) = Proteced for waterfowl, shore birds and other water-oriented wildlife not included in Classes 3A, 3B, or 3C, including the necessary aquatic organisms in their food chain; Class A (West Virginia) = water supply, public; Classes A, A-S, AA, AA-S, B, C, and D (New York) = Classified as fresh surface waters; Class B1 (West Virginia) = warm water fishery streams; Class B3 (West Virginia) = small non-fishable streams; Class B2 (West Virginia) = trout waters; Class C (DC) = Protected for aquatic life, waterfowl, shore birds and water-oriented wildlife; Class E (DC) = Protected for use as a raw water source for industrial water supply; Class GA (New York) = Classified as fresh groundwater; Class GW1 (New Jersey) = Groundwater in the Central Pine Barrens suitable for potable water supply, agricultural water supply, and continual replenishment of surface waters to maintain existing quantity and quality of the surface waters in Central Pine Barrens and other reasonable uses; Class GW2 (New Jersey) = Groundwater, having a natural total dissolved solids (TDS) concentration of 500 mg/L or less, suitable for potable, industrial, or agricultural water supply, after having conventional water treatment where indicated; Class GW3 (New Jersey) = Groundwater, having a natural TDS concentration between 500 mg/L and 10,000 mg/L, suitable for conversion to fresh potable waters, or other beneficial uses; Classes SA, SB, SC, and SD (New York) = Classified as saline surface waters; CWF = cold-water fishery; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GWWF = general warm-water fishery; LWWF = limited warm-water fishery; MAC = maximum allowable concentration; MAL = maximum allowable level; MCC = maximum contaminant concentration; MCL = maximum contaminant level; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Level; RDA = Recommended Daily Allowance; REL = Recommended Exposure Limit; RfD = reference dose; Special Class A (Wyoming) = Suitable for fish and aquatic life; STEL = Short-term Exposure Limit; TLV = Threshold Limit Value; TSCA = Toxic Substances Control Act; TWA = Time-Weighted Average; Water Class A (Minnesota) = Without treatment the raw waters will meet the state's drinking water standards (This standard will ordinarily be restricted to underground waters with a high degree of natural protection); Water Class B (Iowa) = Class B waters are designated for wildlife, fish, aquatic and semi-aquatic life, and secondary contact water uses; Water Class B (Minnesota) = With minimum disinfection the treated water will meet requirements for drinking water (This standard will ordinarily be restricted to surface and underground waters with a moderately high degree of natural protection); Water Class C (Iowa) = Class C waters are designated for raw water sources for potable water supply; Zn = zinc

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9.GLOSSARY

Acute Exposore - Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) - The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) - The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) - The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) - The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen - A chemical capable of inducing cancer.

Ceiling Value - A concentration of a substance that should ndt be exceeded, even instantaneously.

Chronic Exposure - Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity - The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity - Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory - An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) - The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure - Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9.GLOSSARY

Immunologic Toxicity - The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

***In Vitro* -** Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo* -** Occurring within the living organism.

Lethal Concentration $_{(LO)}$ (LC_{LO}) - The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration $_{(50)}$ (LC_{50}) - A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose $_{(LO)}$ (LD_{LO}) - The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose $_{(50)}$ (LD_{50}) - The dose of a chemical which has been calculated to cause death in 50% of a de ined experimental animal population.

Lethal Time $_{(50)}$ (LT_{50}) - A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) - The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations - Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level - An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen - A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity - The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) - The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) - The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

9.GLOSSARY

Permissible Exposure Limit (PEL) - An allowable exposure level in workplace air averaged over an 8-hour shift.

q1 * - The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) - An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) - The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity - The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) - The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity - This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen - A chemical that causes structural defects that affect the development of an organism. Threshold Limit Value (TLV) - A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) - An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) - A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

9.GLOSSARY

Uncertainty Factor (UF) - A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A
USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects by duration of exposure and end point and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

(5). Species The test species, whether animal or human are identified in this column. Species

(6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column This permits comparison of NOARLs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). Reference The complete reference citation is given in Chapter 8 of the profile.

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-1

LSE figures graphically illustrate me data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

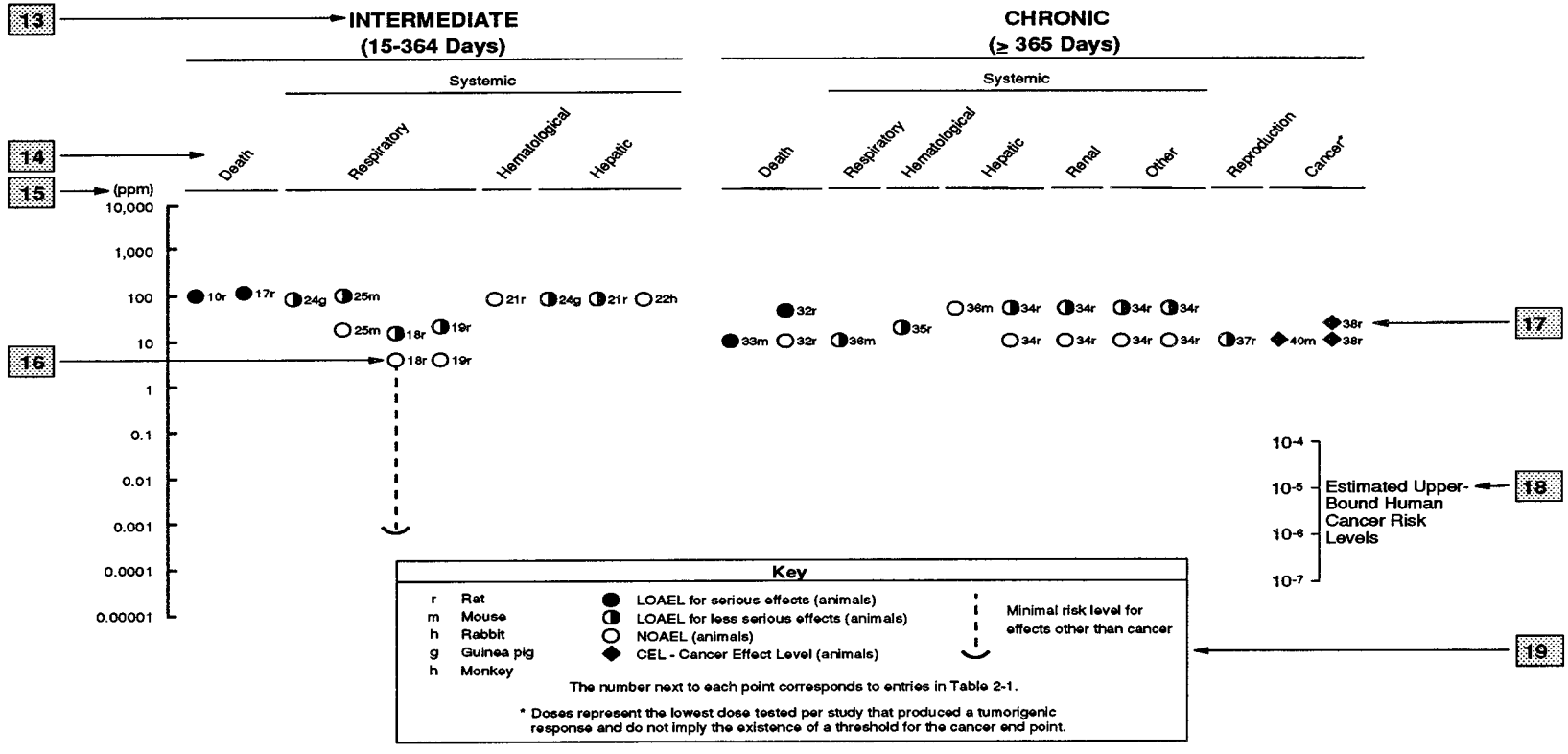
[a] The number corresponds to entries in Figure 2-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

FIGURE 2-1. Levels of Significant Exposure to [Chemical X] - Inhalation



(13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Chemicals” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor of (1, 3, or 10) is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of (1, 3, or 10) are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and (1, 3, or 10) are used for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. Generally an uncertainty factor of 10 is used; however, the MIX Workgroup reserves the right to use uncertainty factors of (1, 3, or 10) based on scientific judgement. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

APPENDIX B

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
M	Molar
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification

SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

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