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Volume 5 of 8

OCCUPATIONAL HEALTH AND SAFETY AND ENVIRONMENTAL ASPECTS OF ZINC CHLORIDE

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Final Report - April, 1978

by

Harriet Glaser Hill, M.S.
Khizar Wasti, Ph.D.

Principal Investigator

Jon E. Villaume, Ph.D.

Reviewed by

Frederick J. Goldstein, Ph.D.

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First Lt. Carl D. Rowlett, Medical Services Corps
Environmental Protection Research Division
U.S. Army Medical Bioengineering Research and Development Laboratory
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This Problem Definition Study provides a literature review (113 references) on occupational health hazards and environmental aspects of zinc chloride which is a major product of a smoke generated from HC (hexachloroethane) mixture for screening purposes and fire-fighting exercises. Included are physical and chemical properties, human and animal toxicity, effects on microorganisms, plants, and aquatic organisms, pharmacokinetics, fate in the environment, industrial safety standards and practices, and sampling and analysis methodology of zinc chloride. Environmental impacts are discussed →

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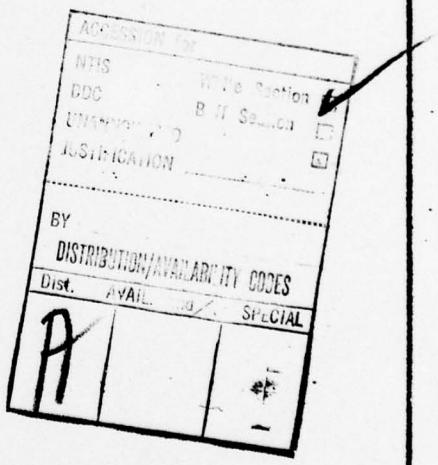
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Human toxicity	Pharmacokinetics	Teratogenicity
Inhalation toxicity	Physical properties	TLV
Industrial hygiene	Plants	Toxicity
Metabolism	Safety practices	Uptake by Aquatic Organisms
Microorganisms	Sampling	Wildlife
Mutagenicity	Smoke	Zinc
Occurrence	Smoke generation	Zinc Chloride
Persistence	Standards	Zinc ion

20. Abstract (continued)

and recommendations for further studies are provided. Zinc chloride is hygroscopic and astringent and has been found to be toxic if inhaled at elevated concentrations or in enclosed spaces with inadequate ventilation. In occupational exposure, contact with the skin, eyes, or nose can cause severe burns. Ingestion of zinc chloride solutions can result in severe gastrointestinal ulceration. No evidence exists in the literature that zinc chloride is mutagenic. Injection of zinc chloride solutions into the yolk sacs of chicken eggs induced teratogenic effects. Teratogenic effects in other species have not been reported in the literature. There have been no reported cases of carcinogenicity due to zinc chloride exposure in humans. Except for the ability to induce teratomas by intratesticular injections in fowl, no experimental evidence exists that zinc chloride administered orally or intraperitoneally is carcinogenic.



EXECUTIVE SUMMARY

Zinc chloride is a white, odorless compound which readily dissolves in water. It has been used by the military as a smoke screen to protect personnel, in metal and textile industries, and for fire-fighting exercises among others.

Zinc chloride smoke is a potential health hazard, especially when generated in an enclosed space with inadequate ventilation. Persons breathing in high concentrations suffer severe pulmonary irritation. The lungs can become filled with fluid and the lung tissue may be destroyed. Extended exposure to high concentrations can be fatal. Skin contact with aqueous zinc chloride solutions causes severe burns especially if contact occurs around a pre-existing wound. Oral intake of zinc chloride paste by a child was reported to produce corrosive gastritis and liver necrosis, and proved fatal. Eye and nose contamination with zinc chloride by 2 workers caused burns on the eyes, permanently impaired vision, and permanent loss of the sense of smell.

Laboratory dogs exposed to high concentrations of zinc chloride smoke developed fluid in their lungs. Application of a solution of zinc chloride to the shaved skin of guinea pigs slowed growth but did not cause deaths. However, an injection of a zinc chloride solution into the abdomens of guinea pigs caused the deaths of 8 out of 10 animals in one week; 6 died within 24 hours. Prolonged oral intake of a solution of zinc chloride in addition to a diet deficient in pantothenic acid, caused vitamin deficiency symptoms and retarded growth in rats. In another study, prolonged oral intake of zinc chloride did not affect reproduction and normal young were born. Rats given intraperitoneal injections of zinc chloride for several weeks developed kidney and nerve cell injuries and abnormalities.

There have been no reported cases of carcinogenicity due to zinc chloride exposure in humans. Except for the ability to induce tumors by intratesticular injections in fowl, no evidence exists that zinc chloride is carcinogenic in animals by oral or intraperitoneal routes of administration.

No evidence exists in the literature that zinc chloride is mutagenic. Zinc chloride has produced teratogenic effects when injected into the yolk sacs of chicken eggs.

Zinc chloride is toxic to freshwater and marine organisms. The toxic concentrations of zinc chloride to fishes vary with species and water conditions. However, concentrations as low as 0.17 mg/l of zinc chloride in water have been found to be lethal. In the embryos of clams, sand dollars, and sea urchins, zinc chloride induced mortalities and abnormal development.

Exposure to zinc chloride and gamma radiation, alone or in combination, decreased the survival of a strain of bacteria. Immersion of corn and tomato leaves and cauliflower, lettuce, and carrot cultures into zinc chloride solutions caused leaf injury and inhibited growth. Zinc is required for normal plant growth but excess concentrations can accumulate and have toxic effects.

Zinc is absorbed through the skin and gastrointestinal tract as evidenced by experiments with radioactive zinc chloride in man and animals. Absorbed zinc is distributed in the tissues with the highest concentrations being found in the liver. The primary route of excretion of zinc was through the feces. In experiments with aquatic organisms, radioactive $zinc^{65}$ was distributed in the tissues of clams, mussels, and sea urchins.

Zinc can accumulate in plants, aquatic organisms, domestic animals and wildlife which are consumed by humans. These represent a possible route for the accumulation of zinc in the food chain. Zinc occurs naturally in rocks, water, plants, animals and man. It is dispersed in the environment by zinc chloride smoke screens and by various industries. Several factors, such as soil condition and climate determine the subsequent movement of zinc and its fate in the environment.

Zinc chloride is produced as a smoke from HC (hexachloroethane) smoke pots. HC smoke mix is a solid mixture of grained aluminum, zinc oxide, and hexachloroethane in percentages of 6.68, 46.66, and 46.66, respectively. The environmental impact of this zinc chloride cloud and resultant fallout are subsequently reviewed.

ABSTRACT

This Problem Definition Study provides a literature review (113 references) on occupational health hazards and environmental aspects of zinc chloride which is a major product of a smoke generated from HC (hexachloroethane) mixture for screening purposes and fire-fighting exercises. Included are physical and chemical properties, human and animal toxicity, effects on microorganisms, plants, and aquatic organisms, pharmacokinetics, fate in the environment, industrial safety standards and practices, and sampling and analysis methodology of zinc chloride. Environmental impacts are discussed and recommendations for further studies are provided. Zinc chloride is hygroscopic and astringent and has been found to be toxic if inhaled at elevated concentrations or in enclosed spaces with inadequate ventilation. In occupational exposure, contact with the skin, eyes, or nose can cause severe burns. Ingestion of zinc chloride solutions can result in severe gastrointestinal ulceration. No evidence exists in the literature that zinc chloride is mutagenic. Injection of zinc chloride solutions into the yolk sacs of chicken eggs induced teratogenic effects. Teratogenic effects in other species have not been reported in the literature. There have been no reported cases of carcinogenicity due to zinc chloride exposure in humans. Except for the ability to induce teratomas by intratesticular injections in fowl, no experimental evidence exists that zinc chloride administered orally or intraperitoneally is carcinogenic.

FOREWORD

The industrial hygiene and occupational health research program of the U. S. Army Bioengineering Research and Development Laboratory, Fort Detrick, Maryland was initiated in 1976 to study health problems and recommend criteria for occupational exposure to military-unique chemicals. This Problem Definition Study (PDS) has been prepared as part of the research program under contract number DAMD-17-77-C-7020 in order to provide published data relating to occupational health and safety, and environmental aspects of zinc chloride smoke. The subjects covered in this report include physical and chemical properties, toxicological studies on humans, experimental animals, aquatic organisms, domestic animals and wildlife, plants, and microorganisms, pharmacokinetic data, environmental fate, industrial hygiene and safety practices, and sampling and analysis methodology.

This Problem Definition Study is the fifth in a series of eight reports prepared under this contract.

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I. INTRODUCTION

Smoke screens are produced by the military to conceal personnel, material or installations and to reduce direct visual observation. HC (hexachloroethane) mixture is one of the numerous compounds used by the military for producing smoke screens. It is also employed in civilian life to simulate actual conditions in firefighting exercises. HC smoke mix is a solid mixture of grained aluminum, zinc oxide, and hexachloroethane in percentages of 6.68, 46.66, and 46.66, respectively. Zinc chloride is the major component of the smoke generated by burning HC mixture. As a result zinc chloride is released into the environment exposing personnel involved in the operations. Zinc chloride is also used in many industries such as textiles, adhesives and cements, metallurgy, and pharmaceuticals.

This Problem Definition Study has been prepared in order to provide an evaluation of the health hazards, safety aspects, and environmental impact of zinc chloride. The present report provides available data on physical and chemical properties, human toxicity, toxicity to experimental animals, wildlife and domestic animals, aquatic organisms, plants, and pharmacokinetics. Industrial hygiene and safety practices, and sampling and anlaysis methodology are also discussed. Environmental aspects covered in this study include occurrence, dispersion, and fate in the environment. No information is available either on the amount of zinc chloride released into the environment or the area covered by the smoke during actual screening operations. However, these two parameters are estimated to establish model concentrations released into the environment by HC smoke generation. These model concentrations of zinc chloride are then compared with known toxic levels in order to assess its potential environmental impact.

Sources examined to locate relevant information in the literature are included in the appendix. In addition, there is a list of organizations contacted to obtain pertinent data on zinc chloride.

II. PHYSICAL AND CHEMICAL PROPERTIES

Zinc chloride is one of the most important zinc salts commercially. It was first prepared by Glauber in 1648, who obtained it as a thick oil by heating sal ammoniac (ammonium chloride) with calamine (zinc carbonate). Zinc chloride has also been known as "Butter of Zinc," because on evaporation hydrated form produces a white semi-solid mass similar in constituency to butter (1,2). The molecular formula, molecular weight, synonyms and other related data for zinc chloride are given in Table 1.

TABLE 1.

Nomenclature and Related Data

Chemical name:	Zinc chloride
Synonyms:	Butter of zinc; zinc butter; zinc dichloride
Chemical Abstract Service (CAS) registry number:	007646857
Registry of Toxic Effects of Chemical Substances number:	ZH 14000 (1976)
Wiswesser line notation (WLN):	.ZN..G2
Molecular formula:	$ZnCl_2$
Molecular weight:	136.27

Zinc chloride is a white, odorless compound which can be obtained as very deliquescent granules, or fused pieces or rods (1-3). It is very soluble in water and organic solvents such as alcohol, acetone, and glycerol. The solutions of zinc chloride are fluorescent. Solid zinc chloride is a poor conductor of electricity while the conductivity of the molten form lies between that of a good and a poor conductor (1). The physical and thermodynamic properties of zinc chloride are given in Table 2.

Zinc chloride was formerly assigned a hexagonal structure (rhombohedral), but recent work has shown that it is trimorphic representing α-, β-, and γ-forms. The commercial product is α-, γ-, or α- plus γ-zinc chloride (1).

It is very difficult to obtain zinc chloride in anhydrous form owing to its deliquescent nature. However, the anhydrous form is remarkably stable to heat. It melts to a clear, colorless, highly refractive liquid, and may be distilled without decomposition up to a temperature of at least 900°C (1).

Commercial zinc chloride is commonly manufactured by the action of hydrochloric acid on zinc scrap, dross, or zinc oxide, and is usually 95% pure. The remaining 5% is chiefly water and some oxychloride ($ZnCl_2.nZnO$) (1,2).

TABLE 2.

Physical and Thermodynamic Properties of
Zinc Chloride

Appearance:	White, odorless, deliquescent granules, or fused pieces or rods.
Density:	2.91 g/cm^3 at 25°C
Melting point:	About 290°C
Boiling point:	756°C at 760 mm Hg
Index of refraction:	1.681
Heat of fusion:	5.54 KCal/mole
Heat of vaporization	28.7 KCal/mole
Heat capacity (Cp):	18.3 cal/mole/degree at 25°C
Heat of formation:	-99.6 KCal/mole at 25°C
Free energy of formation:	-88.45 cal/mole at 25°C
Entropy:	25.9 cal/mole/degree at 25°C
Vapor pressure, mm Hg:	1 5 10 20 40 60 100 200 400 760
(molten zinc chloride) temperature, °C:	428 481 508 536 566 584 610 648 689 756
Heat of solution of one mole of zinc chloride in 400 moles of water:	15.72 KCal at 18°C
Solubility:	
Cold water :	432 g/100 g at 25°C
Hot water :	614 g/100 g at 100°C
Hydrochloric acid:	400 g/100 ml of 2% HCl
Ethanol :	100 g/100 ml at 12.5°C
Glycerol :	50 g/100 ml
Acetone :	very soluble

Ref. 1-5

As a consequence, nearly all grades of commercial zinc chloride yield turbid aqueous solutions due to the presence of some oxychloride (2).

Concentrated aqueous solutions of zinc chloride are very acidic; the acidity diminishes rapidly on dilution (1). The change in pH with concentration for aqueous solutions of zinc chloride is shown in Figure 1.

In aqueous solution, zinc chloride is partly hydrolyzed to form oxychloride and a solution cannot be evaporated to dryness without considerable decomposition of the salt into oxychloride and hydrochloric acid. It can, however, be crystallized as a dihydrate ($ZnCl_2.2H_2O$) (1).

Zinc chloride forms hydrates with 1, 1.5, 2.5, 3, and 4 moles of water. The hydrates do not crystallize from the solution unless the temperature is 28°C or lower. Above 28°C the anhydrous salt is in equilibrium with the solution as shown in Figure 2 (1).

Zinc chloride forms a number of basic salts and amino complexes:

Basic salts	Amino complexes
$ZnCl_2.Zn(OH)_2$	$ZnCl_2.NH_3$
$ZnCl_2.4\ Zn(OH)_2.H_2O$	$ZnCl_2.2NH_3$
$ZnCl_2.6Zn(OH)_2.2H_2O$	$ZnCl_2.4NH_3$
	$ZnCl_2.6NH_3$
	$ZnCl_2.10NH_3$

Zinc chloride also forms additional compounds or complexes with many amines or other organic compounds and double salts, and double salts with many other metal halides. The most important double salt commercially is zinc ammonium chloride, available in two forms ($ZnCl_2.2NH_4Cl$ and $ZnCl_2.3NH_4Cl$) (1).

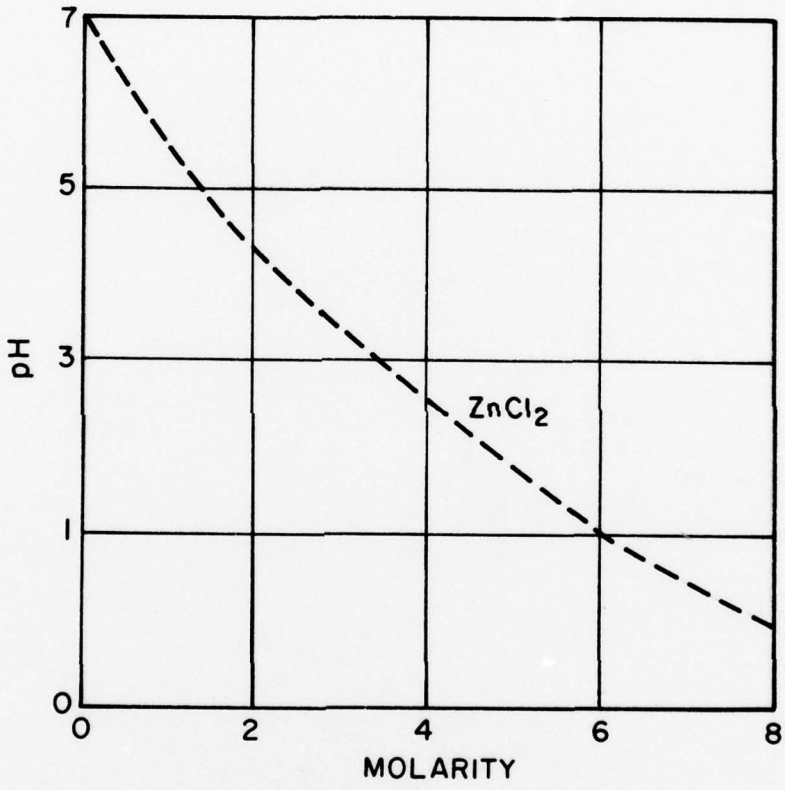


Figure 1. The change in pH with concentrations for aqueous solutions of zinc chloride.

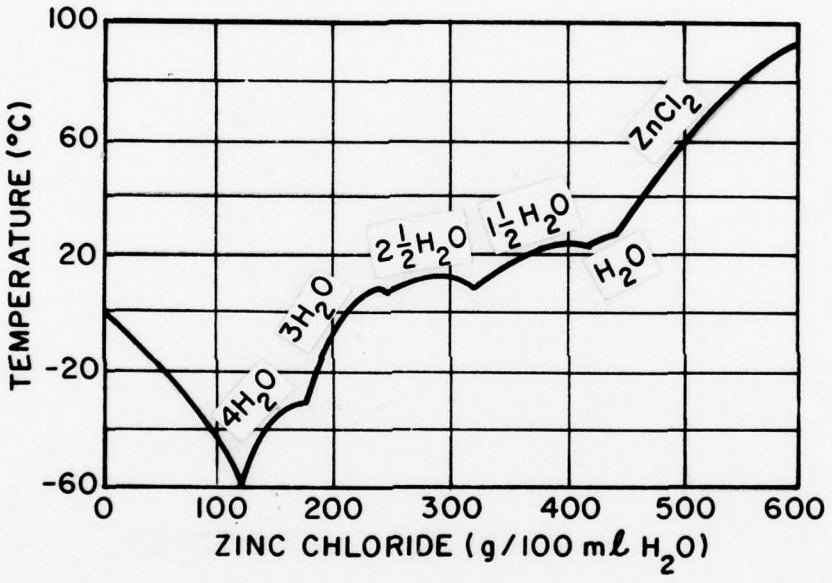


Figure 2. The hydrates of zinc chloride. The hydrates do not separate from the solution unless the temperature is 28° C or lower. Above 28° C the anhydrous salt is in equilibrium with the solution (1).

III. GENERATION OF ZINC CHLORIDE SMOKE

Zinc chloride smoke is generated by the military by using HC smoke pots. Evans (6) reported that in smoke pots used during World War II, hexachloroethane, zinc xoide, and small quantities of calcium silicide and potassium nitrate react to produce a smoke which is mainly a fine cloud of particulate zinc chloride. This is similar to the type of HC smoke bomb described by Cullumbine (7) in which a mixture containing equal quantities of hexachloroethane and zinc oxide, and 10% calcium silicide is ignited. The zinc oxide is reduced to the metal by the calcium silicide. The zinc then reacts with the hexachloroethane to yield free carbon, calcium carbonate, silica, and zinc chloride. Other possible products reported in the literature are carbon dioxide, carbon monoxide, phosgene, hydrocarbons and chlorinated hydrocarbons (10). Cullumbine (7) analyzed the chemical composition of a smoke cloud produced in an enclosed gas chamber. He reported that the cloud contained traces of phosgene and carbon monoxide. For every 100 g of mixture used, a little over 40 g of zinc chloride is released (7).

In a more recent study, Stocum and Hamilton (8) describe a military HC smoke mixture which contains 46.5% zinc oxide, 44.5% hexachloroethane, and 9% grained aluminum. When the HC smoke mixture is heated in a smoke pot, a self propagating reaction is set up which is based, in part, upon the tendency of aluminum to react with hexachloroethane to form aluminum chloride (8,9).

$$2\ Al + C_2Cl_6 \longrightarrow 2\ AlCl_3 + 2\ C + heat$$

The aluminum chloride reacts with zinc oxide to form zinc chloride, as illustrated in the following equation (8,9).

$$2\ AlCl_3 + 3ZnO \longrightarrow 3\ ZnCl_2 + Al_2O_3$$

The overall reaction can be summarized as follows:

$$2\ Al + C_2Cl_6 + 3\ ZnO \longrightarrow 3\ ZnCl_2 + Al_2O_3 + 2\ C + heat.$$

The spread of smoke produced by HC mixture over the area to be obscured is dependent on prevailing winds. The smoke pots are directed to keep screening smokes close to ground level (10). They are usually placed about 70 meters from the target to be screened and have a burning time of 12-20 minutes. Each pot usually has an HC mixture charge capacity of 13.6 kg. Under suitable meteorological conditions, the cloud produced rises to about 16 meters (11). More recently, the United States military has experimented with a vertical screening smoke curtain. The proposed curtain would be deployed within 2-10 seconds, be 185 to 300 meters long, have an altitude of 30 meters from ground level, and persist for 30 seconds. HC smoke grenades (containing 540 g of HC smoke mixture) would be launched from a ground emplaced mortar tube and ignited remotely, using a small blasting machine (A description of the machine was not provided) (10).

IV. HUMAN TOXICITY

Several cases of acute zinc chloride intoxication have been reported, the majority of which occurred in military or industrial environments as a result of inhalation of zinc chloride smoke. However, intoxication from skin contact and fatalities following accidental ingestion of zinc chloride have also occurred. The chronic toxicity of zinc chloride has not been well documented.

A. ACUTE EFFECTS

The acute toxic effects of zinc chloride smoke inhalation are given in Table 3 (page 22). The effects of skin, eyes, and nose contact, and ingestion of zinc chloride are summarized in Table 4 (page 26).

1. Inhalation

Symptoms of zinc chloride intoxication, which are typical of almost all reported cases of inhalation of high concentrations of zinc chloride smoke, include dyspnea, a feeling of constriction in the chest, retrosternal and epigastric pain, hoarseness, stridor, lachrymation, cough, expectoration, and, occasionally, hemoptysis. Pale grey cyanosis, and reddening of the conjunctiva, nasopharynx, and larynx are also described. Victims are usually agitated and restless with fever and elevated pulse rate. Bronchopneumonia usually develops. Death is generally due to shock or respiratory insufficiency (12).

The most potent noxious factor is the hygroscopic or astringent nature of the compound. Fumes from chemicals, such as zinc chloride, are retained in the alveoli by their combination with mucous secretions. Simple edema develops around the hilar region and is associated with a generalized alveolar consolidation uniformly distributed throughout the lung. This condition becomes evident upon radiographic examination. The severity of pulmonary edema caused by irritation of the bronchus by zinc chloride and similar smokes depends upon the concentration to which the patient has been exposed (13).

Zinc chloride smoke is also caustic to mucous membranes and can produce subacute interstitial fibrosis which generally appears shortly after exposure (concentration not specified) (14). Inhalation of zinc chloride smoke is most dangerous indoors or in enclosed spaces with inadequate ventilation. However, minor symptoms lasting a few hours have been reported after exposure in the open (concentration not specified). These symptoms include minor respiratory discomfort, tightness in the chest, a slight cough, and dry throat (6).

Volunteers exposed to atmospheres containing 120 mg/m^3 of zinc chloride smoke complained of nose, throat and chest irritation, cough and nausea after 2 minutes. After 2 minutes at 80 mg/m^3, most had slight nausea, a few coughed, and all could smell the smoke. However, when men working in a field were exposed to smoke (concentration not specified) for 30 minutes at a distance 27 meters from the source, the only complaint was a slight burning sensation in the chest (7). It should be pointed out that the OSHA standard for zinc chloride fume is 1 mg/m^3 in air.

Accidental cases of zinc chloride smoke intoxication have been documented in the literature.

Whitaker (13) described the case of a 20-year-old sailor who suffered acute respiratory distress with dyspnea and cyanosis following exposure to a smoke screen that contained zinc chloride (concentration and length of exposure were not specified). Symptoms appeared immediately and intensified in the hours following exposure. A radiograph revealed shadowing due to simple edema confined mainly to the central zone of the lung, and discrete mottling. Cardiac enlargement and prominence of the pulmonary artery were evident. The patient's lungs did not return to normal until more than 2 months after exposure. The persistence of the unusual radiological appearance was attributed to alveolar involvement. The caustic, minute zinc chloride particles which were retained in the alveoli caused a local inflammatory reaction and appreciable damage to the alveolar epithelium (13).

Post-mortem examination of the lungs of 2 victims who died 6 and 11 days after exposure to zinc chloride smoke (concentration and duration of exposure not reported) revealed necrotizing tracheitis, bronchitis, and confluent bronchopneumonia with thrombosis, chronic pneumonia, and bronchiolitis obliterans (15).

Evans (6) reported an incident of massive exposure to zinc chloride smoke when 79 smoke pots were ignited at the mouth of a tunnel and burned for one-half hour. The smoke produced by these generators consisted of fine particulate zinc chloride with carbon particles and carbon dioxide. Seventy persons were exposed to atmospheric concentrations of approximately 120 g/m^3 of smoke near the pots; 34 persons were treated, of whom a total of 10 died. All victims experienced dyspnea, feeling of tightness in the chest, retrosternal and epigastric pain, stridor, and red and running eyes. Most complained of a cough with abundant and often blood-stained mucous secretions; cyanosis was evident. Acute inflammation of the respiratory tract persisted for 7-10 days and often developed into bronchopneumonia. Autopsies of two victims revealed edema of the laryngeal, tracheal and bronchial mucosa. The brain and abdominal viscera were acutely congested. One victim had liver, brain, and kidney congestion (6).

Exposure to zinc chloride smoke (concentration not specified) caused respiratory difficulty, increasing tachypnea, a feeling of constriction in the chest, sore throat and hoarseness, grey cyanosis, and painful cough in a 35-year-old fireman (16). The victim complained of nausea due to possible stomach irritation. Interstitial pulmonary fibrosis, acute cor pulmonale, and right ventricular hypertrophy developed. The patient died of acute respiratory insufficiency 18 days after exposure (16).

Lumsden and Weir (17) reported subglottic stenosis in a 28-year-old man exposed to zinc chloride screening smoke after a generator had exploded (concentration and exposure time were not estimated). The condition was accompanied by generalized edema of the larynx, arytenoids and ventricular bands, and redness of the vocal cords. The patient developed bronchitis with pneumonitis and tonsillitis. Tracheotomy and dilatation of the larynx were required. The patient recovered 13 1/2 months after the accident.

Nine other persons were exposed in this accident, 3 of whom died. The conditions of the 6 remaining men were not described (17).

MacAulay and Mant (18) presented the case of a 19-year-old soldier who died 11 days after exposure to a high concentration of zinc chloride smoke for 4 minutes (concentration not given). Exposure occurred during a Civil Defense exercise in which a smoke canister was ignited in a stable in order to simulate a fire. The victim's initial symptoms included severe retrosternal pain, vomiting, abdominal cramps, a foul taste in his mouth, anxiety and cyanosis. Twenty-four hours after admission, his temperature reached 102°F, his pulse rate increased to 120 and he became increasingly cyanotic. Chest X-rays revealed acute pulmonary edema and a blood count revealed leucocytosis. His condition worsened and on the fifth day, fine crepitations were evident in the lung. X-rays on the seventh and ninth days revealed extensive bronchopneumonia. The patient did not respond to therapy and expired 11 days after exposure. Subsequent investigations revealed severe interstitial and alveolar fibrosis in the lungs accompanied by necrosis, squamous metaplasia of the cells lining the large bronchi, and detachment of the epithelium of smaller bronchi. A culture of pus in the bronchial tree produced a pure growth of *Asperigillus fumigatus*. Quantitative chemical examination showed the equivalent of 92.9 mg of zinc in the left lung (6.73 mg/100 g of tissue) (18).

Pare and Sandler (19) described the case of an 18-year-old soldier who was exposed to a high concentration of zinc chloride smoke in a house for 10 minutes (concentration not available) during an Army exercise. A nonproductive cough, shortness of breath, lethargy and vomiting were noted. One day after exposure, the patient experienced a severe nasal hemorrhage. On admission to the hospital, a fever of 99-100°F was noted and the patient complained of shortness of breath and a pain in his side. Moist crepitations of both lungs were audible and the air entry was markedly diminished. Other symptoms typical of zinc chloride intoxication were not present. The most striking physical sign was poor expansion of the chest. A chest X-ray revealed patchy consolidation of all areas of both lungs. The patient recovered and left the hospital 6 weeks after the accident (19).

Johnson and Stonehill (20) reported 3 cases of chemical pneumonitis from the inhalation of zinc chloride. All 3 were airmen in their late teens. The patients experienced over-exposure to 4075 mg/m^3 of zinc chloride smoke, which was produced by the combustion of zinc oxide, grained aluminum, and hexachloroethane grenade. Aluminum chloride (334 mg/m^3), aluminum oxide (134 mg/m^3), and zinc oxide (108 mg/m^3) were also found by analysis of an air sample at the scene of exposure and may have also contributed to the toxicity. The concentration of the total particulate matter was 800 mg/m^3 and the average particle size was 0.1 micron (range 0.01 - 25 microns). In all 3 patients, the initial symptoms included nausea, paroxysmal cough, dyspnea, and tightness of the chest. These symptoms were no longer evident 6 hours after exposure following "conservative" medical care. Later symptoms, including fever, tachypnea, and cyanosis developed. Coughing became less frequent and nonproductive, but X-rays revealed marked parenchymal infiltration. Vital lung capacity was diminished, but returned to normal. Throat, blood, and sputum cultures, and no evidence of prolonged leukocytosis or productive cough ruled out bacterial pneumonitis. All 3 patients recovered within one month (20).

Stocum and Hamilton (8) have reported effects of exposure to zinc chloride smoke based on the zinc chloride smoke concentrations and duration of exposures given in the previously described case histories. These effects are summarized in Table 3.

TABLE 3.

Effects Produced by Zinc Chloride Smoke Inhalation

Concentration (mg/m^3)	Duration (minutes)	Dosage Producing Effect ($mg\text{-}min/m^3$)[a]	Effects Produced
80 - 120	2	160 to 240	Nose, throat and chest irritation, cough, nausea
190 to N.A.	9 N.A.	1,700 to 2,000	Marked throat irritation, some lung congestion, usually requiring hospitalization, observation and treatment
4100	N.A.	20,000	Severe respiratory irritation leading to "chemical pneumonia", requiring aggressive treatment
N.A.	N.A.	50,000	Massive respiratory tract injury; may be fatal; death due to shock & pulmonary edema
120,000	N.A.[b]		

[a] dosage = concentration x exposure time

[b] smoke generators burned for 30 minutes but exposure time may have been shorter.

N.A.-concentration and/or duration not specified

Ref.: Stocum and Hamilton, 1976 (8)

2. Cutaneous Toxicity

When personnel are exposed to zinc chloride smoke, some skin contact would be unavoidable. However, no reports dealing with this problem have been located in the literature. The cutaneous toxicity of zinc chloride when encountered in industry will be discussed.

Zinc chloride has been used to treat railway ties because of its fire resistance and fungicidal action (21). Due to its caustic action, skin contact may cause burns and lesions of the forearms, fingers, and hands of workers (22).

McCord and Kilker (21) reported the development of skin lesions and burns on the hands and fingers of 10 men who handled treated railway ties. These lesions generally developed at the site of a recent injury such as abrasion, burn, chapping, or splinter. The severity of the zinc chloride lesions was dependent upon the length of exposure and the size of the antecedent injury.

3. Eye and Nose Toxicity

Exposure to zinc chloride smoke can cause eye and nose irritation (23). This toxicity however, has only been described briefly. In industry, contact with zinc chloride could arise from the use of galvanizing solutions or soldering paste. Houle and Grant (23) presented one case of accidental eye contamination and one of eye and nasal contamination in two workers using one of these two preparations. The soldering paste contained 30% of zinc chloride, 30% monoethanolamine hydrochloride, and 10% each of polyethylene glycol, ammonium chloride, zinc oxide and water. Application of a 30% monoethanolamine hydrochloride solution on the eye of a volunteer did not produce injury, and the authors suggest that zinc chloride was the only toxic ingredient in the soldering paste. The other ingredients of the galvanizing solution were not known but the mixture had a pH of 3.53 which, alone, could have produced the injury (23).

The eye injuries were characterized by corneal edema, and some permanent corneal scarring. Both patients developed cylinder refractive errors, and persistent gray spots were evident beneath the anterior lens capsules. One lens slowly, but progressively developed corneal opacities. Recovery to the best stable visual acuity was unusually slow, taking 6-28 weeks. The nasal injury caused mucosal lesions and bilateral obstruction. The patient permanently lost his sense of smell which was attributed to zinc chloride's ability to damage nerve endings (23).

4. Oral Toxicity

Oral intake of zinc chloride, due to its corrosive action can cause gastrointestinal perforation and ulceration. Jacobziner and Raybin (24) described the fatal case of a 6 1/2-year-old boy who ingested soldering paste containing 96 percent zinc chloride. The child was immediately given large amounts of warm milk and water, which caused repeated vomiting. However, he complained of abdominal pain, was unable to retain any foods or liquids, and was admitted to the hospital 24 hours after ingestion. A total gastrectomy was performed revealing necrosis of the entire stomach from the esophogus

to the pylorus and moderate distention of the colon. The patient continued to vomit, became very restless, pale, and cyanotic. He lapsed into a coma and died 9 days after ingesting paste. Autopsy findings revealed corrosive gastritis and hepatic necrosis (24).

Severe cases of food poisoning developed in 25 of 42 men who had eaten cooked apples prepared and served in a galvanized iron kettle. Chemical analysis revealed 83 mg of zinc in 100 g of apples and 17 mg of zinc in 100 g of vomit (25). A similar case was reported in an institution in London. Four hundred persons ingested hot stewed apples prepared in a galvanized iron kettle. Within minutes, 200 persons became ill complaining of dizziness, sickness, and tightness in the throat; some developed diarrhea. High concentrations (not reported) of zinc were detected in the apples (26).

Jacobziner and Raybin (24) have reported the characteristic symptoms of intoxication resulting from ingestion of zinc chloride. Symptoms include salivation; edema of the glottis; difficulty swallowing; massive swelling of the lips; pain in the mouth, throat, and epigastrum; recurrent violent vomiting; severe abdominal pain; and bloody diarrhea. A rapid but weak pulse, a drop in blood pressure, stertorous respirations, and cold, clammy skin are usually evident. Muscular weakness or spasms, aphonia, and sensory disturbances may occur in some cases. Death is generally due to circulatory collapse and shock from peritonitis which results from perforation of the gastrointestinal tract. Damage to the kidney accompanied by albuminuria, hemoglobinuria, and an oliguria may occur if death does not occur within several hours (24).

B. CHRONIC EFFECTS

Cases of prolonged exposure to zinc chloride smoke have not been reported in the literature. There are no studies available on chronic effects of zinc chloride ingestion. However, water in galvanized pipes or vessels often dissolves the zinc coating, and, as a result, zinc is ingested. One report describes symptoms of chronic cutaneous toxicity. The effects of chronic exposure to zinc chloride (cutaneous, eye, nose, and systemic toxicity) are included in Table 4.

1. Cutaneous Toxicity

DuBray (27) reported the case of chronic zinc intoxication in a 34-year-old man who worked as a renovator operator in a mattress and pillow factory and, consequently, over a 4-year period, had exposed his hands to an aqueous zinc chloride solution (concentration not specified) which was used in the renovator. The symptoms included fatigue, weight loss, pain in the long bones, and anorexia (27).

2. Oral Toxicity

Swim et al. (28) suggested that the amount of zinc ingested and converted to zinc chloride in the stomachs of shinglers, roofers, or lathers who are accustomed to "mouthing" galvanized shingle nails, was too small to cause local gastrointestinal irritation. It was estimated that an average of 80 mg of zinc per nail was ingested from "mouthing" 10 nails.

In a review article Bartow and Weigle (29) reported that zinc sometimes occurs in tap water having been dissolved from the zinc coating of galvanized iron pipes and tanks. Underground waters from zinc mines may contain considerable concentrations of zinc and concentrations as high as 550 mg/1 zinc have been reported in waters from mines and mills. These waters usually have a strong astringent taste and, as a result, are generally not ingested by men or animals. Persons have been reported to drink water containing 23 mg/1 zinc for prolonged periods (exact time not reported) without adverse effects. On the other hand, ingestion of zinc-containing water (concentration not specified) from a fountain for 30 days caused fainting spells, cramps, and nausea. Symptoms disappeared when the zinc coating was removed from the pipes supplying the fountain. Persons drinking water containing 5-8 mg/1 zinc for several weeks reportedly became ill. Details of the illness are not provided. The galvanized water-supply pipes had been newly installed and symptoms disappeared when the pipes were thoroughly flushed several times (29).

TABLE 4.

Effects of Exposure to Zinc Chloride:
Cutaneous, Eye and Nose, and Systemic Toxicity

Toxicity	Formulation	Concentration	Effect	Reference
CUTANEOUS	Zinc chloride railway treatment	N.A.	skin lesions and burns generally at the site of recent injury e.g., abrasion burns, chapping or splinters.	McCord and Kilker, 1921 (21)
OCULAR	Zinc chloride soldering paste/galvanizing solution	N.A.	Corneal edema; permanent scarring; development of cylinder retractive errors, persistent gray spots beneath the anterior lens capsule; corneal opacities.	House and Grant, 1973 (23)
NASAL	Zinc chloride galvanizing paste	N.A.	Lesions of the nasal mucosa; bilateral nasal obstruction; permanent loss of sense of smell.	Ibid
SYSTEMIC	Soldering paste	96% $ZnCl_2$	Fatal; abdominal pain; vomiting; necrosis extending from esophogus to pylorus; distention of colon; cyanosis. Autopsy revealed corrosive gastritis and hepatic necrosis.	Jacobziner and Raybin, 1962 (24)
	Concentrated aqueous zinc chloride solution	N.A.	Fatigue; weight loss; pain in long bones; anorexia.	DuBray, 1937 (27)

N.A.-Not Available

V. OCCUPATIONAL HEALTH AND SAFETY PRACTICES AND STANDARDS

The health hazards and risks of exposure to zinc chloride as smoke screens have been well-documented in the literature. Several cases of zinc chloride smoke intoxication and fatalities during World War II have been reported in the literature. These, as well as the previously discussed cases of eye and nose injury, dermatitis, and ingestion of zinc chloride, clearly point out the need for appropriate protective measures. The recommended standards for zinc chloride exposure, protective measures during use, and exposure limits of zinc chloride smoke will be reviewed in the following sections.

A. FEDERAL EXPOSURE LIMIT

The Occupational Safety and Health Administration (OSHA) of the United States Department of Labor has set the limiting concentration of 1 mg/m^3 in air for zinc chloride fumes. The OSHA standards are 8-hour time-weighted averages not to be exceeded in any 8-hour shift of a 40-hour work week (30).

B. PROTECTIVE MEASURES

Persons working around zinc chloride fumes should wear protective equipment. Eye and face protection, protective clothing, and respiratory protective equipment are recommended (31). Mechanical filtration of inspired air by means of a self-contained breathing apparatus can provide protection for personnel exposed to zinc chloride smoke. This device can maintain positive facepiece pressure and is able to provide adequate protection for cumulative exposures of at least 60 minutes. It is recommended, however, that persons using the self-contained breathing apparatus receive at least 5-6 hours of training including: a) wearing the unit for a long period; b) familiarization with mobility limitations due to the size of the device; c) full familiarization with operation of the apparatus including safety features. Personnel should be briefed on the effects of zinc chloride exposure, especially the early symptoms and the importance of terminating the exposure if these early symptoms become evident (8).

Where the risk of direct contact with zinc chloride exists, application of protective ointments prior to work acts as a mechanical barrier. The contaminants are washed off with the ointment (32). Small amounts of zinc chloride which do come into contact with a worker's hands are not easily removed by ordinary soap and water; washing with a 5% solution of hydrochloric acid will be effective (27). Protective gloves and clothing, such as acid-proof and water-proof overalls, and canvas gauntlets, which will not interfere with job performance, are also recommended (21,32)

If eye, skin, or mucous membrane contamination does occur, prolonged irrigation with water or a 15-minute irrigation with neutral 0.05 M EDTA solution should begin immediately (23). All contaminated clothing should be removed and the patient should be placed in a "deluge-type" shower as quickly as possible if the contaminated area is large (4). To decrease the risk of zinc chloride burns, skin abrasions should be adequately protected and minor injuries to the hands and forearms should receive prompt treatment (21).

Zinc chloride should be stored in tightly closed containers in a well-ventilated place. When handling, safety glasses, a dust mask, and rubber gloves should be worn. Proper disposal of the chemical includes slowly placing it into a large container of water and gradually adding soda ash while stirring gently. After 24 hours, it can be siphoned or decanted into another container, neutralized with 6 M hydrochloric acid, and drained into the sewer with abundant water. Spills or leaks should be swept into a beaker and diluted with ample water. Soda ash and hydrochloric acid should be added as previously described before draining into the sewer with abundant water (5).

C. EXPOSURE LIMITS OF ZINC CHLORIDE SMOKE

In view of the data available to date it appears that personnel exposed to zinc chloride screening smoke can avoid the adverse effects provided they remain at a certain distance from the source. Cullumbine (7) has calculated that under suitable meteorological conditions, in a good area, and at a given zinc chloride concentration, certain "safety distances" exist. Persons can safely stay at that distance for a definite time period termed the "safety time". These safety times and distances will differ during the day and at night due to meteorological conditions as illustrated in Table 5.

TABLE 5.

Safe Distances and Times of Zinc Chloride Smoke Exposure

	Distance from Source (Meters)	Estimated Zinc Chloride Concentration (mg/m^3), at given distances from the source	Safety Time
Day	91	47 mg/m^3	43 minutes
	914	0.9 mg/m^3	37 hours
Night	183	85 mg/m^3	24 minutes
	914	13 mg/m^3	2.5 hours

Ref. Cullumbine, 1957 (7)

VI. TOXICITY TO EXPERIMENTAL ANIMALS

The acute and chronic effects of zinc chloride using experimental animals as models have not been thoroughly investigated despite the wide use and potentially toxic nature of zinc chloride as documented in the Human Toxicity Section. The acute and chronic toxic effects of inhalation, ingestion, percutaneous and ocular application and intraperitoneal injection of zinc chloride on experimental animals are summarized in Table 6 (page 34). Chemical interactions of zinc and other metals are discussed briefly.

A. ACUTE EFFECTS

Inhalation of zinc chloride smoke caused pulmonary irritation in mice and dogs. Percutaneous application of an aqueous solution of zinc chloride caused no mortalities in guinea pigs but did retard growth. Application of concentrated zinc chloride solution to eyes of rabbits induced severe corneal damage. Intraperitoneal injection of aqueous zinc chloride caused mortalities in guinea pigs. These studies will be reviewed in this subsection.

1. Inhalation

Reports on the effects of inhalation of zinc chloride smoke by mice and dogs are presented.

a. Mice

Cullumbine (7) reported that the dosage of zinc chloride smoke required to kill 50% of exposed mice (LC_t50) was estimated to be 11,800 mg-min/m^3. At 2,000 mg-min/m^3, macroscopic or histological lung damage was no longer evident.

b. Dogs

Ardran (33) undertook an experimental radiographic investigation of the pulmonary effects of zinc chloride smoke inhalation. Five dogs weighing 6-13 kg were exposed to high concentrations (exact concentration not specified) of hexachloroethane smoke, the active constituent of which is a fine cloud of zinc chloride particles. The animals were exposed for an average of 20 minutes. Hemoconcentration developed after the radiological appearance of pulmonary edema and returned to normal within a few days. Mottled edema appeared first in the apex of the cardiac lobes and gradually extended over the whole of both lung fields. Lung volume increased following exposure but returned to normal as the edema subsided (33).

2. Percutaneous Application

Percutaneous application of zinc chloride on the shaved skin of 20 guinea pigs caused reduced weight gain but had no other toxic effect (34). Two milliliters of 0.239 M aqueous solution of zinc chloride were applied once to a 3.1 cm^2 exposure area which was then covered. No mortalities were caused by percutaneous application of zinc chloride for 3 weeks. However, the exposed animals gained weight only during the first post-treatment week, whereas controls gained weight continuously over an 8 week observation period (34).

3. Ocular Application

Eye application of a concentrated zinc chloride solution in the eyes of albino rabbits weighing 0.6-1 kg induced severe corneal damage (35). In one group, the rabbits were anesthetized intravenously and a 50% zinc chloride solution (volume not specified) was applied to both eyes simultaneously. Corneal opacification became evident four days to two weeks after treatment and also became ulcerated and perforated. During the 2-week observation period, a considerable discharge developed in some rabbits which made the eyelids stick together. The authors suggest that the zinc chloride induced eye injury is associated with denaturation of the corneal stroma, which is measured by a reduction in water absorbing capacity of the stroma, and is associated with persistent binding of zinc to the stroma (35).

4. Oral Administration

The acute oral median lethal dose of zinc chloride in mice, rats, and guinea pigs has been reported as 350, 350, and 200 mg/kg of body weight, respectively (36). No other effects were described.

The oral average lethal dose of zinc chloride in rats and rabbits has been reported as 750 and 1000 mg/kg, respectively (37).

a. Rats

Seventy-six rats (sex, strain, and weight not reported) were given a single oral dose of 2, 5, 10, 20, or 50% zinc chloride solution by gavage in sufficient volumes to yield doses of 500, 750 and 1000 mg/kg. The animals were observed for 11 days. Thirty-one rats died within 24 hours of administration. The average oral lethal dose of zinc chloride for rats was 750 mg/kg and was independent of the concentration used. Necropsies revealed perforation of the stomach or penetration into the liver tissue and pyloric stenosis. In those animals dying first, mucosal damage was less evident but tremor, ataxia, dyspnea, and a drop in body temperature appeared (37).

b. Rabbits

A similar experiment was conducted in rabbits (sex, strain, and weight not specified). Twelve rabbits received a single oral dose of 5 or 20% zinc chloride solution in sufficient volume to yield doses of 250, 500, and 1000 mg/kg and were observed for 13 days. The average oral lethal dose of zinc chloride to rabbits was determined to be 1000 mg/kg. Necropsy revealed symptoms similar to those previously described for the rats (37).

5. Intraperitoneal Injection

Toxic effects of intraperitoneal injection of zinc chloride in rats and guinea pigs are presented.

a. Rats

The average lethal dose of zinc chloride in rats was determined to be 100 mg/kg by Hahn and Schunk (37). A total of 8 rats (sex, strain, and weight not reported) were given single intraperitoneal injections of 50 or 100 mg/kg

zinc chloride (observation period was not specified). Five animals died between 5 hours and 5 days after injection. The validity of the lethal dose is questionable because only 2 out of 5 rats were injected with 100 mg/kg and both died 5-12 hours after injection. Symptoms were not described.

b. Guinea pigs

The effects of intraperitoneal injection of zinc chloride in guinea pigs were investigated by Wahlberg (34). Ten guinea pigs (average weight 374-380 g) were given single intraperitoneal injection of 2.0 ml of a 0.239 M aqueous solution of zinc chloride (about 170 mg/kg BW). The animals were observed for 7 days. After 24 hours, 6 of the 10 guinea pigs had died; 2 more animals died 7 days after treatment. No other effects were studied.

6. Subcutaneous Injection

The average subcutaneous lethal dose of zinc chloride in rats was determined to be 1000 mg/kg (37). Twelve rats (sex, weight and strain not specified) were given single subcutaneous injections of 500 or 1000 mg/kg zinc chloride. One animal out of six injected with 500 mg/kg zinc chloride died 7 hours after injection while 2 died after 12 and 34 days. Five of six rats injected with 1000 mg/kg died 12 hours to 3 days after treatment. Symptoms were not described (37).

B. CHRONIC EFFECTS

Chronic oral administration of zinc chloride had no effect on reproduction but did precipitate vitamin deficiency syndrome in rats. Intraperitoneal injection of zinc chloride in rats caused morphological changes in the renal tubules and central nervous system. These chronic studies are presented.

1. Oral Administration

The effects of chronic ingestion of zinc chloride on reproduction and nutrition of rats have been investigated.

a. Effect on reproduction

Ingestion of dietary zinc chloride had no toxic effect on the reproduction and offspring of rats (38). The rats were maintained on a basal diet containing 2.5 to 5 g/kg zinc (as zinc chloride) and were allowed to breed. Zinc chloride ingestion had no apparent effect on growth, mating, or the number of young born. The offspring appeared healthy and were continued on the same treatment. When mated, they produced normal, vigorous offspring. An autopsy performed after full growth had been reached revealed no lesions or other pathological conditions. Tissue analysis revealed no significant increase in zinc content as compared to controls (38).

b. Effect on nutrition

Zinc has been shown to be an essential metal for the nutrition of the rat, and a deficiency can prove harmful. Prolonged ingestion of large

amounts of zinc, however, can also be toxic. Gross et al. (39) have suggested that the lipid solubility and higher reactivity of zinc chloride accounts for its high toxicity as compared to other zinc salts. Chronic zinc chloride intoxication can precipitate a pantothenic acid deficiency in albino rats (39).

Young female rats (21 to 24 days old; average weight 40 g) were fed a synthetic diet; a filtrate fraction low in pantothenic acid; a vitamin supplement consisting of thiamin chloride, riboflavin, pyridoxine, rich polish factor II, nicotinic acid, and ethyl linoleate; and 4-6 mg of zinc chloride by gavage for 20 weeks. Deficiency symptoms developed which included growth retardation and severe alopecia, especially on the face, head, neck, back, and abdomen. The normally white fur developed rusting and a ruffled appearance. Control rats given the identical diet without zinc chloride exhibited somewhat reduced weight gain and some rusting of the fur, but no additional symptoms developed. When the daily diet was supplemented by 150 µg of calcium pantothenate per day, the deficiency syndrome subsided even though zinc chloride intake was continued. If zinc chloride was mixed directly with the diet, its toxic effects were lost (39).

Black rats fed 5-6 mg of zinc chloride in oil under the same conditions previously described showed severe greying. Crusting of the nose, chin, tail, and eyelids was evident. Symptoms generally appeared 3 to 5 weeks after treatment began (39).

Six groups of 4 rats were fed the same vitamin-deficient diet, 100 mg of filtrate fraction, a vitamin supplement, and 4-15 mg/day zinc chloride in oil. In addition, the rats were also administered a daily dose of 100 µg calcium panththenate. Only a slight toxic effect was evident after 4 weeks. Therefore, the dose of zinc chloride was increased to 75, 100, 125, 150, 200, and 250 mg/kg body weight. By the sixth week, weight gains declined and rusted fur became evident (39).

2. Intraperitoneal Injection

Intraperitoneal injection of zinc chloride solutions has been shown to affect the kidneys and central nervous system of rats.

a. Effect on the kidneys

Intraperitoneal injections of zinc chloride resulted in morphological kidney tubule changes in rats. Fazzari and Catini (40) investigated the effects of sub-lethal concentrations of zinc chloride on the renal tubules of 1-year old 250 g male and female Wistar rats. They were given intraperitoneal injections of 1.2 mg zinc chloride in normal saline on alternate days for 20 days. Modification of the epithelium of the proximal and distal convoluted tubules and the loops of Henle were observed. Nuclei of the cells of these tubules appeared to have increased to greater than 3 to 4 times their normal size. Stained material (Feulgen) appeared distributed along the nuclear membrane while the central area appeared clear and almost "emptied". Nuclear material was found throughout the cytoplasm. Granular cytoplasm was evident in cells with normal nuclei which contained stained and evenly distributed material. However, a small, amorphous body appeared in both

normal and abnormal nuclei. The cytoplasm of abnormal cells appeared vacuolized and had no affinity for acidic or basic stains. The epithelial cells of the proximal tubules resembled the "edges of a brush" appearing fragmented and irregularly distributed. The authors suggest that injection of sub-lethal concentrations of zinc chloride induced a potentially toxic and irreversible modification of the renal tubules, especially of the nuclei of the renal tubular epithelium (40).

b. Effect on the central nervous system

Fazzari and Catini (41) found that intraperitoneal injections of zinc chloride affected the motor neurons of the spinal cord. Two groups of 10 Wistar strain rats (both sexes) each received injections of 0.6 or 1.2 mg zinc (as zinc chloride) in normal saline (pH 6.9-7.1) on alternate days for 20 days. Paresis of the hind-legs and anal sphincters developed but disappeared within a few hours. Morphological changes of the neurons, especially in the anterior columns and lumbar horns, were evident after 20 days. There was a notable increase in the cytoplasmic and nuclear basophil material (41).

C. CHEMICAL INTERACTIONS

Several metals and chemicals have antagonistic or synergistic effects on zinc toxicity. A diet containing 0.7% zinc caused anemia and growth depression in rats. The anemia could be prevented and alleviated by administration of 0.2 mg copper per day. The growth depression was not corrected by the copper but by the administration of liver extract. Zinc uptake by bone was reduced by administration of calcium and phosphorus. The addition of 0.04% zinc (as zinc oxide) to a diet containing 200 mg/kg molybdenum decreased weight gain to 52% of that seen in rats given molybdenum alone (42). Total-body turnover of zinc 65 in mice was not affected by the administration of copper, gallium, or magnesium, but administration of cadmium consistently increased zinc retention (43).

TABLE 6.

Effects of Zinc Chloride in Experimental Animals

Route of Administration	Dose	Length of Exposure	Effects	Reference
ACUTE EFFECTS				
1) INHALATION:				
Dogs	N.A.	20 minutes	Hemoconcentration; mottled pulmonary edema extending over the whole of both lung fields	Ardan, 1950 (33)
Mice	11,800 mg-min/m^3	N.A.	LC_t50	Cullumbine, 1957 (7)
2) PERCUTANEOUS APPLICATION:				
Guinea Pigs	2 ml of 0.239 M aqueous solution	single dose	Reduced weight gain	Wahlberg, 1965 (34)
3) INTRAPERITONEAL INJECTION:				
Guinea Pigs	2 ml of 0.239 M aqueous solution	single dose	6/10 mortalities within 24 hours; 2 more deaths by day 7	Ibid
Rats	100 mg/kg	single dose	Average lethal dose	Hahn and Schunk, 1955 (37)
4) OCULAR APPLICATION:				
Rabbits	50% zinc chloride solution	single dose	Corneal opacification; corneal ulceration and perforation; some discharge	Johnstone et al., 1973 (35)
5) ORAL ADMINISTRATION:				
Mice	350 mg/kg	single dose	LD_{50}	Browning, 1969 (36)
Rats	350 mg/kg	single dose	LD_{50}	Ibid
Guinea pigs	200 mg/kg	single dose	LD_{50}	Ibid
Rats	750 mg/kg	single dose	Average lethal dose	Hahn and Schunk, 1955 (37)
Rabbits	1000 mg/kg	single dose	Average lethal dose	Ibid

TABLE 6. (continued)

Effects of Zinc Chloride in Experimental Animals

Route of Administration	Dose	Length of Exposure	Effects	Reference
6) SUBCUTANEOUS INJECTION:				
Rats	1000 mg/kg	single dose	Average lethal dose	Ibid
CHRONIC EFFECTS				
1) ORAL ADMINISTRATION				
Rats	0.25-0.5%	chronic (duration of administration not specified)	No effect	Heller and Burke, (38)
Rats	4-6 mg in olive oil	daily for 20 weeks	Rusting or greying of coat; crusting of the nose, chin, tail, eyelids; severe alopecia; growth retardation. Symptoms resembled pantothenic acid deficiency.	Gross et al., 1941 (39)
2) INTRAPERITONEAL INJECTION:				
Rats	1.2 mg in normal saline	alternate days for 20 days	Modifications of epithelium of loops of Henle, distal and proximal convoluted tubules; lysed cells due to nuclear eruption; vacuolized cytoplasm	Fazzari et al., 1966 (40)
Rats	0.6-1.2 mg in normal saline	alternate days for 20 days	Temporary paresis of hind legs and anal sphincters; morphological changes of motor neurons of spinal cord	Fazzari et al., 1968 (41)

N.A. -Not Available

LC_t50-Median lethal dosage (concentration x exposure time)

LD_{50} -Median lethal dose

VII. EFFECTS ON DOMESTIC ANIMALS AND WILDLIFE

Studies on the effects of zinc chloride on domestic animals are limited to reproduction and development of chick embryos. Data on the toxicological effects of exposure of other domestic animals and wildlife to zinc chloride have not been located in the literature. However, ingestion of dietary zinc and zinc-containing water (as total zinc) by domestic animals has been reported and will be presented in this section.

A. ORAL TOXICITY

The oral toxicity of zinc to domestic animals varies with the species and often with the composition of the diet. Pigs and poultry exhibit a tolerance to dietary zinc, while sheep and cattle are less tolerant.

1. Poultry

Poultry are highly tolerant of dietary zinc but the toxicity may vary with diet. Prolonged ingestion of 1200-1400 mg/kg by broilers and laying hens had no adverse effects. When the zinc level was raised to 3000 mg/kg, reduced growth and appetite depression were evident. Diet composition, however, influences zinc toxicity (44). Baby chicks fed 2000 mg/kg zinc (as zinc oxide) with corn-soybean, corn-fish meal, or sucrose-soybean diets for 2 weeks showed no ill effects. But when the zinc was added to a sucrose-fish meal diet, reduced weight gain was evident. As little as 800 mg/kg zinc was found to be toxic (44).

2. Swine

Swine are also highly tolerant of dietary zinc. Chronic ingestion of 0.9 to 50 mg/l zinc in ground and surface waters had no adverse effects (28). Weanling pigs fed diets containing 1000 mg/kg zinc (as the sulfate and carbonate) for several weeks showed no ill effects. Higher zinc levels depressed growth and appetite, and arthritis and internal hemorrhages were evident. A high mortality rate was observed at 4000 and 8000 mg/kg zinc. It is interesting to note that an increase in dietary calcium levels from 0.7 to 1.1% in pigs administered 4000 mg/kg zinc counteracted the toxic effects of the zinc (44).

3. Sheep

Sheep are less tolerant of zinc than poultry and pigs. Reduced weight gains, decreased feed efficiency, and depressed feed consumption were evident in lambs fed diets containing 1000 and 1500 mg/kg zinc (as zinc oxide) (44). Ingestion of 700 mg/kg of zinc by ewes resulted in a high incidence of perinatal deaths. Intake of high levels of zinc induced tissue changes in sheep including subnormal liver copper levels, mild anemia, and changes in rumen metabolism (44).

4. Cattle and Horses

Cattle are also less tolerant of zinc than pigs and poultry. The relative tolerance of zinc by horses was not reported. Horses and cattle can ingest

0.9-50 mg/l zinc without toxic effects (44). Ingestion of grass containing 500 mg/g zinc is not likely to be toxic to cattle (45). A diet containing 500 mg/kg zinc or less had no effect on steers or heifers. However, 900 mg/kg zinc caused reduced weight gains and lowered feed efficiency, while 1700 mg/kg induced an abnormal appetite with excessive salt consumption and wood chewing. At higher levels, tissue changes similar to those described for sheep were evident (44).

B. YOLK INJECTION

The effects of environmental pollutants on avian reproduction and development are primarily dependent upon 1) the levels of contamination in food sources, 2) the rate at which the contaminants ingested by egg-laying females are incorporated into the eggs, 3) and the actions of stored toxicants on fecundity, fertilization, and embryonic development (46). Birds have a tendency to concentrate ingested metals in their eggs and avian embryos are highly sensitive to trace metals. Zinc may appear in trace amounts in avian food sources and may, consequently, accumulate in the eggs (47).

Exposure of newly laid eggs to zinc chloride can decrease hatchability and survival, and can induce significant teratogenic effects (44). Two hundred white Plymouth Rock strain chicken eggs (*Gallus domesticus*) were treated by yolk injection with 1.0 ng/g-50.0 µg/g zinc (as zinc chloride) in 0.1 ml aliquots of distilled water immediately prior to incubation (47). The eggs were then incubated through hatching at 38°C, 60-65% humidity. Control eggs were injected with 0.1 ml of distilled water. The percent survival was measured as hatchability of exposed eggs/controls. Control hatchability ranged from 75% to 86% and averaged 81%. The percent survival of treated eggs decreased as the zinc concentration increased, ranging from 83% at a concentration of 1 ng/g to 9% at 10 µg/g. Injection with 50 mg/kg caused 100% mortality. The percent of anomalous birds increased as the zinc concentration increased, ranging from 2% at 0.1 mg/kg to 29% at 10.0 mg/kg. The most frequent changes included brain deficiencies, absent eyes, skeletal anomalies, unabsorbed yolk sacs, and, most commonly, severe locomotor impairment. Hydrocephaly, acephaly, and absent beaks were occasionally observed. The median tolerance limit (TL_{50}) for zinc (as zinc chloride) was calculated to be 1.0 mg/kg. No anomalies were reported for the control group (47).

In a similar study, the effects of yolk injections with 1:1 mixtures of zinc (as zinc chloride) and either cadmium (as cadmium chloride) or mercury (as mercuric chloride) were investigated. The experimental design was the same as that previously described except 10 mg/kg was the highest concentration injected. The percent survival of eggs injected with a 1:1 mixture of zinc and cadmium was 78% at a concentration of 1 ng/g and 24% at 1.0 mg/kg; 100% mortality occurred with 5.0 mg/kg. Control hatchability averaged 83%. Zinc and mercury mixtures were less toxic, 80% surviving treatment with 1 ng/g and 8% surviving with 10.0 mg/kg. The authors suggested that two-way combinations of zinc, mercury, and cadmium exert purely additive effects on chick hatchability and no discernible antagonistic interactions were evident (46).

VIII. MUTAGENICITY, CARCINOGENICITY, AND TERATOGENICITY

Ingestion, intratesticular injection, intraperitoneal, intratracheal, and subpleural administration of zinc chloride induced the development of only a small number of tumors in the experimental animals. However, no figures of statistical significance were reported in any of the studies. Injection of zinc chloride into newly laid poultry eggs induced significant teratogenic effects.

A. MUTAGENICITY

No evidence was found in the literature available to date that zinc chloride is mutagenic.

Zinc chloride was tested for its mutagenic potential by rec-assay (48). *Bacillus subtilis* strains H_{17} (Rec^+, arg^-, trp^-) and M_{45} (Rec^-, arg^-, trp^-) were exposed to 0.05 M zinc chloride in distilled water. Zinc chloride did not inhibit bacterial growth and showed no mutagenicity (48).

Sirover and Loeb (49) measured the ability of zinc chloride to affect the accuracy of DNA synthesis *in vitro*. Using DNA polymerase from avian myeloblastosis virus, which has a "propensity to make mistakes", the effect of zinc chloride on the fidelity of DNA synthesis was determined at concentrations between 20 µM and 150 µM. Zinc chloride did not affect the accuracy of DNA synthesis but did decrease its rate of synthesis (49).

Hoffman and Niyogi (50) examined the effects of zinc chloride on the rate of initiation of RNA synthesis and overall RNA synthesis using calf thymus DNA and phage T_4 DNA as templates. Zinc chloride, which is not considered to be mutagenic, inhibited chain initiation of RNA synthesis at concentrations that inhibited overall RNA synthesis. The mutagenic compounds on the other hand, stimulated chain initiation of RNA synthesis (50).

B. CARCINOGENICITY

There have been no reported cases of carcinogenicity due to zinc chloride exposure in humans.

Studies on the potential carcinogenic effects of zinc chloride have been conducted with rodents and fowl. Investigations involving oral administration and skin contact are limited. Most of the experiments have been performed utilizing intratesticular injections of aqueous zinc chloride solutions. The results of these studies will be reviewed in this section.

1. Oral Administration

Tumor development was observed in mice following chronic ingestion of zinc chloride. De Szilvay (51) conducted a series of experiments in which mice (sex, strain, and age not reported) ingested potable water (*ad libitum*) containing different concentrations of zinc chloride for 5 or more months. The mice developed pulmonary adenomas, mammary, uterine, bone marrow and other cancers within 5-8 months. The experimental details and results are given in Table 7.

In another experiment, 5 groups of 20 mice were given water containing 0-100 mg/ml of zinc chloride (51). The experiment lasted 3 years and all offspring born during that period were also maintained on the same drinking water. Sixteen percent (16/100) of the original mice died due to either seminomas, uterine cancer, mammary or lung cancer. Thirty percent (30/100) of the offspring also died due to sarcomas, leiomyomas, pulmonary adenomas, fibrosarcomas, and granulosa cell tumors. The data indicate that tumors occurred more frequently in the offspring than the parents. The frequency of tumors increased with each generation and the time of tumor induction decreased. In addition, the rate of zinc accumulation and the toxicity of zinc chloride both increased with each generation. The incidence of tumors in controls was not discussed (51).

2. Intratesticular Injections

Experimentally induced teratomas following intratesticular injections of zinc chloride were reported in the literature as early as 1926. Testicular tumors in fowl could only be induced during the period of gonadal growth, which is January through March in northern latitudes (36). Similar experiments with rats and hamsters have been less successful.

a. Rodents

Intratesticular injections of aqueous zinc chloride solution into mice and rats failed to induce testicular teratomas. There is a report indicating that zinc chloride induced embryonal carcinoma in hamsters but this cannot be regarded as conclusive, since there were no controls used in the study.

Twenty-seven 7-week-old CFW mice were given intratesticular injections of 1% or 2% aqueous zinc chloride solution (volume of injection not specified) into testes which were either normally situated or had been surgically transplanted into the abdominal position. The animals were sacrificed 102 to 116 days after treatment. No tumors were induced by zinc chloride injections but other changes were evident which included hemorrhage, inflammation, necrosis, and inhibition of spermatogenesis (52).

In a similar experiment, adult golden hamsters were given intratesticular injections of 1, 2, or 5% zinc chloride (volume of injection not specified). Testes were either normally situated in the scrotum or surgically transplanted into an abdominal position. Injection with 5% zinc chloride killed most hamsters within 24 hours.

Groups of eighteen and ten hamsters were given single intratesticular injections of 1% and 2% aqueous solutions (volumes of injection not specified), respectively. The animals were sacrificed 99-102 days after injection. No tumors were noted but those treated with 1% zinc chloride showed localized hemorrhage, inflammation, and infarction with necrosis. Animals treated with a 2% solution exhibited an inflammatory reaction with extensive localized necrosis (52).

TABLE 7.

Tumor Development in Mice after Administration of Zinc Chloride in Drinking Water for 5-8 Months

Expt.	Number of Animals	Zinc Chloride Concentration (mg/l)	Number of Animals with Tumors	Pathological Findings
I[a]				
Experimental	100	10-20	10	seminoma; bone marrow and uterine cancer.[d]
Control	40	0.016 mg/l zinc	0	hepatic and suprarenal necrosis
II[b]				
Experimental	75	10-20	9	pulmonary adenoma; hemangioma; uterine and bone marrow cancer.
Control	25	0.016 mg/l zinc	2	pulmonary adenoma; hemangioma
III				
Experimental	100	10-20 mg + cigarette smoke[c]	4	pulmonary adenoma; lung, mammary, and uterine cancer.
Control	50	cigarette smoke only	1	pulmonary adenoma; epithelial metaplasia of bronchial mucosa

[a] tumor-resistant strain of mice

[b] offspring of tumor-susceptible mice

[c] animals were maintained in glass cage saturated with cigarette smoke

[d] type of uterine cancer not specified

Ref. DeSzilvay, 1964 (51)

In a later experiment, Guthrie and Guthrie (53) gave 49 two-month-old Syrian hamsters (random-bred strain) intratesticular injections of 0.05 ml of 4% aqueous zinc chloride. Injections were given under pentobarbitone (Nembutal) anesthesia during the first 6 weeks of the year when rapid seasonal testicular growth occurs. The hamsters were sacrificed and necropsied in late April and early May. No controls were used in this study (53).

Necropsies revealed 6 cases in which no testes were evident (53). In 3 of these cases, fibrous-walled cavities near the epididymis indicative of total testicular destruction were noted. In the remaining 43 hamsters, areas of coagulative necrosis were produced by the injection. Embryonal carcinomas were found adjacent to these areas of necrosis in the left testes of 2 animals sacrificed 10 weeks after treatment. These tumors were characterized by giant cells, large and convoluted nuclei, prominent nucleoli, and the absence of spermatogenesis in the seminiferous tubules (53).

Guthrie (54) investigated the carcinogenicity of zinc chloride when injected into the normally situated right testes of rats. Twenty-nine 3-month-old rats were injected with 0.15 ml of a 5% aqueous solution of zinc chloride. No testicular tumors were evident when the rats were sacrificed at 18 months of age. However, inoculated testis showed extensive tubular hyalinization with some calcification. Sertoli cells with degenerate spermatozoa were noted in a few seminiferous tubules; and moderate numbers of interstitial cells were present (54).

b. Fowl

In one of the earlier studies, Bagg (55) investigated the effects of intratesticular zinc chloride treatment in young and adult roosters which had received injections of gonad-stimulating hormones.

Thirty adult hybrid roosters (average weight 1.7 kg) were injected with 0.25-0.4 ml, depending upon the size of the organ, of 5% aqueous zinc chloride solution during the first 3 months of the year (55). Only the left testes was treated and the other served as a control. In some cases, birds given intratesticular injections of Ringer-Tyrode solution, served as controls. Four birds died within 1 to 3 days of treatment. Autopsy revealed intense inflammation, edema, and hemorrhage at the injection site. In birds that were sacrificed or had died 80 days after treatment, areas of necrosis and evidence of blood clots were found. After 80 days or more, lesions were described as being fairly well healed while the testes, though partly deformed, showed active spermatic "function". Two birds, surviving 95 and 98 days, respectively, developed teratomas of the treated testes. Both had received 0.3 ml injections in 2 equal 0.15 ml parts. These tumors were described as an "adult type" and were characterized by extensive cartilage formation. Both were firm and were covered with variably sized, fluid filled cysts. Glandular tissues, ducts lined with epithelium, embryonal connective or fat tissue, smooth or striated muscle, feather follicles, and, occasionally, nervous tissue were evident in the tumors. No metastases were evident in the tumors and attempts at heterotransplantation were unsuccessful. However, areas of epithelium with carcinomatous and adenocarcinomatous structures (structures not described) were noted in the treated testes (55).

Eleven birds, which had survived this experiment and which had not developed tumors, were given a second injection into the left testis with approximately the same dose of zinc chloride previously used followed by 2 injections of chorionic gonadotropin (follutein; 46 rat units per bird). This was followed by 7 injections of an extract of the precipitate of urine of a human testicular tumor patient. Finally, each bird was given a 0.30 ml of 5% aqueous zinc chloride solution in the right testis. The birds were autopsied 309-430 days after treatment. No tumors were found (55).

In a subsequent experiment, 35 adult roosters were given intratesticular injections of zinc chloride and injections of one of several hormones; and 22 birds received hormone alone (55). The hormones included teratoma testis hormone, sheep anterior pituitary extract, Parke-Davis antuitrin, chorionic epithelioma hormone, and follutein. No tumor formation was evident in chemically treated testis. However, 2 white Leghorn cockerels which were injected with zinc chloride following prolonged treatment with human pregnancy urine, follutein, and anterior pituitary extracts developed testicular tumors similar to those previously described. In a follow-up study, birds were injected with 5% zinc chloride before, after, or during experimental hormone stimulation. This treatment failed to produce teratomas. In all experiments, control birds or control testes did not develop tumors (55).

Carleton et al. (56) studied the histiogenesis of experimentally induced testicular teratomas. Hampshire Red, Barred Rock, White Leghorn, White Brainered, Austrolorp, and Delaware roosters, 3 months to 18 months old, were given injections of 0.2 to 0.5 ml of a 5% aqueous zinc chloride solution into the pole of the right testis. Fifty percent of the roosters were sacrificed at intervals from one to twelve weeks after treatment, and the remainder were sacrificed monthly up to 9 months after the injections. A total of 350 birds were autopsied.

Tumors were found in birds in all groups but the highest incidence was found in the White Leghorns given injections of zinc chloride (dose not specified) at 18 months of age. Eleven tumors were encountered in 43 White Leghorns killed 3 to 9 months after treatment. The incidence of tumors in the remaining groups was not reported. Hemorrhagic necrosis of the testicular parenchyma was evident immediately following injection. The neoplastic process began in the tubules immediately adjacent to the necrotic parenchyma. The neoplasms took the form of a "monocellular proliferation" resembling a germinoma or embryonal carcinoma found in dogs and man, and were detected 10 weeks after injection. By the third month the growths had spread beyond the tubules as carcinomas and teratoid differentiation became evident. The range of structures which were identified in these teratomas was similar to those found in human teratomas. Dermoid and epidermoid cysts, enteric and genitourinary glands, immature neuroepithelium, myoepithelial and chondroglandular complexes, mature ganglion cells and glia, cartilage and bone, fat and thyroid were described. These carcinomas ultimately led to the development of adult teratomas. No controls were used in the experiment (56).

Guthrie (57) administered intratesticular injections of a 5% zinc chloride solution (0.001 g zinc/g testis) in distilled water into both testes of 57 White Leghorn cocks, age 9-10 months, during the first 3 months of the year. Five birds developed testicular tumors 10-22 weeks after the initiation of treatment. No controls were used in the study.

In a later experiment, Guthrie (58) induced testicular teratomas in 65 Japanese quail (*Coturnix coturnix japonica*) which were given intratesticular

injections of 3% aqueous zinc chloride (0.0006 g Zn/g testis). Injections were given into both testes for one week during a period of photoperiodically stimulated testicular growth. Fifteen quail died within 12-24 hours of injection. Necropsy revealed moderate to severe intratesticular hemorrhages. The remaining 50 quail were sacrificed 8-10 weeks after the beginning of treatment and in 2 quail, teratomas were found in right testes. No controls were used in the experiment (58).

Similar experiments and comparable results have been reported by Smith and Powell (59) and Falin (60).

C. TERATOGENICITY

Injection of zinc chloride into the yolks of newly laid White Plymouth Rock strain chicken eggs induced serious teratogenic effects. The most frequent changes included brain deficiencies, absent eyes, skeletal changes, unabsorbed yolk sacs, severe locomotor impairment, hydrocephaly, acephaly, and absent beaks (46). Experimental details are given in Chapter VII - Effects on Domestic Animals and Wildlife.

IX. EFFECTS ON AQUATIC ORGANISMS

The toxic effects of zinc chloride have been investigated in several marine and freshwater species. *Daphnia* were extremely susceptible to zinc chloride during their molting stage. Experiments with freshwater fishes indicate that the toxic concentrations of zinc chloride vary with the species and dissolved oxygen content. Zinc chloride in marine systems caused mortalities in clams, abnormal cleavage, abnormal development, and lysis of sand dollar and sea urchin embryos. A summary of the toxic effects is given in Table 8 (page 49). Interactions of zinc with other trace metals are reviewed.

A. FRESHWATER TOXICITY

The toxic effects of zinc chloride in freshwater species are presented.

1. Diatoms

The 96-hr LC_{50} of zinc chloride for the diatom, *Nitzschia linearis* was reported to be 4.3 mg/1 (water temperature 16-20°C) (61).

2. Crustacea

The crustacean, *Daphnia magna* is considered to be representative of the susceptibility of predominant zooplankton to toxic substances. Anderson (61) carried out a series of experiments to determine the threshold of toxicity of zinc chloride for *Daphnia*. Young daphnids (4 ± 4 hours old) were exposed to different concentrations of zinc chloride in Lake Erie water for 64 hours. *Daphnia* are apparently more susceptible to toxicants during the molting stage which usually occurs at 20 ± 4 hours of age. The duration of exposure, therefore, allowed most individuals to pass through 2 molting stages. The lethal threshold, which is defined as the toxicant concentration that begins to cause mortality for *Daphnia magna* was 1.5 mg/1 (61a).

3. Mollusca

The 96-hr LC_{50} of zinc chloride for the snail, *Physa heterostropha* was reported to be 0.79-1.27 mg/1 (16-20°C) (61).

4. Fish

Chen and Selleck (62) proposed a kinetic-model for the toxicity threshold of zinc chloride to fish. The authors postulated that the processes of toxification and detoxification could achieve an apparent steady-state if the concentrations of toxic substance were not too high. The "toxicity threshold" was determined with one-month-old *Lebistes reticulatus* (common guppy). The fish were exposed to 0.10-1.55 mg/1 of zinc as zinc chloride in a continuous flow

system in which environmental conditions were kept constant. Twenty-five fish from the same brood were exposed to each concentration. The threshold concentration of zinc was determined to be 0.33 mg/1 in a 96-hour experiment under the following conditions:

pH	7.10 - 7.40
Dissolved O_2	8.5 - 8.9 mg/1
Temperature	24.0 - 24.5°C
Flow Rate:	
Dilution water	200 ml/min
Toxicant	2 ml/min
Mean retention Time of test Solution in test chamber	40 minutes

The percent survival decreased as the exposure time and concentration increased. For example, at a concentration of 0.4 mg/1 approximately 95% of the fish survived a 50-hour exposure period. However, at 1.0 mg/1, less than 35% of the exposed fish survived (62).

Sreenivasan and Raj (63) investigated the toxicity of zinc chloride in the fish, *Tilapia mossambica* (5.0-6.0 cm - average size). The 48-hour maximum lethal concentration (LC_{100}) was determined to be 20-22 mg/1 and the median lethal concentration (LC_{50}) was 10-15 mg/1 when the water temperature was 25.8-28.5°C, pH 7.1-7.5, alkalinity was 33.6-48.8 mg/1 (measured as HCO_3^- and not as calcium carbonate), dissolved oxygen was 5.6-8.2 mg/1, and free carbon dioxide was 0.9-1.8 mg/1. It is interesting to note that the addition of 200 mg/1 of calcium chloride to the water reduced the toxicity of zinc chloride by 75%, while increasing the water's oxygen content to 12.3 mg/1 reduced the mortality of *Tilapia* to 40%.

Cairns and Scheier (64) also found that the threshold values of toxicants depended on environmental conditions such as dissolved oxygen. Oxygen concentration during daylight hours may be 8-9 mg/1 (presumably eutrophic conditions) but can drop as low as 2 mg/1 during the night when no photosynthesis occurs (65). The toxicity of zinc chloride to bluegill sunfish, *Lepomis macrochirus* Raf., a widely distributed species, was compared at "normal" (5-9 mg/1) and periodic low (2 mg/1) dissolved oxygen concentrations. The oxygen concentration was decreased 2 hours per day over a 96-hour period. Temperature was maintained at 18°C. Periodic reduction of oxygen diminished the 96-hour median lethal concentration (LC_{50}) from 8 mg/1 to 5 mg/1. In addition, the range between the highest concentration allowing survival and the lowest concentration causing death was markedly reduced (64).

Young carp *(Cyprinus carpio)* exposed to 1 mg/1 of zinc chloride in tap water died within 24 hours. Since tap water is chlorinated, the presence of chloride ions may have affected toxicity. Exposure to 17.1 mg/1 of zinc chloride in stabilized tap water had no detrimental effect on minnows (species not reported) (66). In another study, the maximum concentration of zinc chloride tolerated by young eels, *Anguilla rostrata,* for more than 50 hours was 0.14 mg/1, and 0.65 mg/1 as zinc killed eels in about 12 hours (66). The median lethal concentration (LC_{50}) of zinc chloride to harlequin fish *(Etheostoma histrio)* was estimated to be 0.17 mg/1 (66a).

The time required to reach the median lethal concentration of zinc (as ionic zinc) decreased as water temperature increased. *Lepomis macrochirus* exposed to 5.6 mg/l ionic zinc at 20°C for 96 hours exhibited no mortalities. When the water temperature was increased 1°C/hr, the LC_{50} was 10 mg/l and was reached in 42 hours. However, when the temperature was increased 1.5°C/hr, the LC_{50} of 10 mg/l ionic zinc was reached in 9.3 hours. In the same experiment, the LC_{50} at 20°C was 32.0 mg/l ionic zinc in 12 hours. At 30°C the 5.6 mg/l ionic zinc killed 50% of *Lepomis macrochirus* in 4 hours. The LC_{50} at 30°C was 32.0 mg/l and was reached in 4.7 hours (61).

The lowest concentration of ionic zinc to cause a response in the movement patterns of *Lepomis macrochirus* over a 96-hour period was determined to be 2.94-3.64 mg/l. In another study *Lepomis macrochirus* exposed to 2.4 mg/l zinc (as ionic zinc) for 96 hours suffered no mortalities. The 96-hr LC_{50} was 4.2 mg/l ionic zinc and 5.9 mg/l killed all fish in 96 hours (all tests were at 16-20°C, 5.9 mg/l dissolved oxygen) (61).

Fundulus heteroclitus exposed to 157-180 mg/l zinc chloride became sluggish in 2 hours and died after 24-48 hr (20°C, 24% salinity). The LC_{50} was calculated to be 66 mg/l zinc chloride between 48 and 192 hours. *Fundulus* could tolerate 43 mg/l zinc chloride for 192 hr (20°C). The 48-hr LC_{50} for *Lepomis macrochirus* was reported to be 5.2 mg/l zinc chloride (as ionic zinc; 24°C, soft water). The 96-hr LC_{50} for *Lepomis macrochirus* exposed to zinc chloride was reported as 2.86-3.78 mg/l (16-20°C). In another study, the 24, 48, and 96-hr LC_{50} for *Lepomis* was reported to be 7.24, 7.24, and 5.37 mg/l zinc chloride, respectively. *Ictalurus nebulosus* exposed to up to 12 mg/l zinc chloride showed no adverse effects after 14 days. Adult *Brachydanio rerio* exposed to 8.0 mg/l ionic zinc (as zinc chloride) for 96 hours exhibited no adverse effects. The 48-hr LC_{50} for adult *Brachydanio* was 28.0 mg/l zinc chloride while the 48-hr LC_{50} for eggs was 105.0 mg/l. Minnows (species not reported) exposed to 10 mg/l zinc chloride were killed in 48 hours. A concentration of 16.0 mg/l zinc chloride killed all eels (*Anguilla* sp.) in 20 hours. Fish (species not reported) exposed to 100 mg/l zinc chloride in hard water exhibited no mortalities in 4 days. Mummichogs *(Fundulus heteroclitus)* exposed to 200 mg/l zinc chloride in fresh water were killed in 2 days but exhibited no mortalities when exposed to the same concentration in seawater. A concentration of 1000 mg/l zinc chloride killed trout (species not reported) in 24 hours (61).

The median lethal concentration of zinc chloride in fish will vary depending on the size of the exposed fish. The 96-hr LC_{50} for small, medium, and large *Lepomis macrochirus* was reported to be 7.45, 7.20, and 6.91 mg/l zinc chloride (water temperature 16-20°C) (61).

Toxic concentrations of zinc compounds cause adverse changes in the morphology and physiology of fish. Cellular breakdown of the gills and possible clogging of some with mucus are related to acutely toxic zinc concentrations. In contrast, chronically toxic concentrations of zinc compounds cause general enfeeblement and widespread histological changes to many organs except gills. "Growth and maturation are retarded" (67).

B. MARINE TOXICITY

The toxic effects of zinc chloride to marine mollusks and echinodermata are presented.

1. Mollusca

Calabrese and Nelson (68) studied the effects of zinc chloride on the survival and development of embryos of the hard clam, *Mercenaria mercenaria*. Fertilized clam eggs were exposed to 10 different concentrations of zinc chloride in synthetic seawater medium (25% salinity) at pH 7.0-8.5 and 26 ± 1°C. The exact concentrations used, however, were not reported. Tests were initiated within one hour after fertilization and were terminated after 42 to 48 hours. By this time, the embryos would have developed into straight-hinged larvae and embryonic development would have been completed. The concentration of zinc as zinc chloride, that produced 0 and 100% mortality (LC_0 and LC_{100}, respectively), were determined by actual observation and the concentration producing 50% mortality (LC_{50}) was estimated. The following values were obtained (68):

LC_0	0.095 mg/1	
LC_{50}	0.166 mg/1	(0.138-0.175)
LC_{100}	0.25	

2. Echinodermata

Zinc chloride has also been shown to modify the development pattern of sand dollars *(Dendraster excentricus)* (69). Newly fertilized eggs or 6-hour blastulae were exposed to 0.9-1360 mg/1 of zinc chloride in seawater continuously for 24 hours or for 6, 18, or 24 hours, followed by return to seawater. The temperature was maintained at 18 ± 1°C. It was found that high concentrations of zinc chloride inhibited cleavage. Low concentrations, however, did not have a marked effect on cleavage, but did significantly change the developmental pattern. Exposure of newly fertilized eggs to high and intermediate concentrations of zinc chloride for 24 hours or continuously caused the development of larvae with radial symmetry and poor elongation. Continuous exposure to 1.7 mg/1 and above during cleavage prevented the differentiation of skeleton. In most larvae exogastrulae developed in 10-25% of the larvae at 13.6 mg/1. Continuous exposure after cleavage prevented skeletal differentiation. Exogastrulae developed in 10-25% of the larvae exposed to 13.6 mg/1. In addition, concentrations which were previously inhibitory permitted stomodaea development. When newly fertilized eggs were exposed to high and intermediate concentrations for the first 24 hours followed by return to seawater, the larvae exhibited radial symmetry, poor elongation, and differentiation of apical and basal lobes. Finally, exposure for 6 hours immediately after cleavage caused the development of radial symmetry (69).

Several metallic salts are natural constituents of seawater. Waterman (70) investigated the effects of increased concentration of metallic salts including zinc chloride, on the developmental stage of the sea urchin, *Arbacia punctulata*. The experiment was conducted at room temperature during

July and August. Blastulaes were exposed to zinc chloride in seawater for 17 hours. To test the rate of action of zinc chloride, a culture of embryos was transferred from a 100 mg/l dilution to fresh seawater every 5 minutes. No additional experimental details were provided (70).

Concentrations as low as 2.5 mg/l of zinc chloride inhibited gastrulation of most embryos (70). At 8 mg/l and above, mortality increased and only an occasional attempt at gastrulation was observed. Persistent fertilization membranes and the inability of embryos to escape were described at high concentrations. Finally, at 10 mg/l of zinc chloride gastrulation occurred and many embryos died. When returned to fresh seawater, surviving organisms underwent abnormal development, forming "large globular structures without gut or skeleton" and with irregularly shaped, lethargic ectoderms. When blastulae were exposed to 100 mg/l of zinc chloride for 5-minute intervals, the toxic effects were manifested very quickly after exposure. Fertilization membranes did not disappear and, when partial escape occurred, the embryos did not differentiate (70).

In a similar study, Lallier (71) exposed sea urchin *(Paracentrotus lividus)* eggs to various concentrations of zinc chloride for different periods of time (exposure time not specified). The eggs were treated immediately after fertilization. Up to a concentration of 41 mg/l of zinc chloride, the eggs did not divide into the various stages. If embryos reached the blastula stage, they were immediately lysed. At a concentrations of 13.6 mg/l of zinc chloride, the blastulas appeared later than in controls, were hyperciliated, and became cloudy rapidly. The ectoderms were thickened and this thickening extended toward the vegetative pole. The endoderm was absent and the primary mesenchyme was represented by only a few cells. When eggs were exposed to 13.6 mg/l of zinc chloride for a given time and then washed in seawater, their survival time increased but they exhibited a series of interesting anomalies such as highly developed ciliature, thickened ectoderm, and absence of the endoderm and secondary mesenchyme. The intensity of the treatment directly influenced the differentiation of the primary mesenchyme. Short exposure, in effect, altered the mode of grouping of the mesenchymal cells. These cells formed highly branched, interlaced spicules. Longer exposure caused marked disorganization and cloudiness. When the eggs were exposed to lower concentrations (1.4 mg/l to 2.7 mg/l), the ectoderm formed buds primarily in the vegetative region. Finally, when exposed to 0.14-0.28 mg/l zinc chloride, the dominant, characteristic morphology was hyperdevelopment of the oral lobe, short anal arms, and branched spicules (forming a bushlike network). The endoderm was present with 3 typical segments but the mouth was absent (71).

C. CHEMICAL INTERACTIONS

Certain metals can act synergistically or antagonistically on the toxicity of zinc. Fish in soft water could tolerate 8 mg/l of zinc for 8 hours, but when exposed to 1 mg/l of zinc plus 0.025 mg/l of copper, most fish died within 8 hours. Similar experiments were attempted in hard water (320 mg/l as calcium carbonate) with rainbow trout *(Salmo gairdneri)*. However, no synergy between copper and zinc was evident. Zinc and cyanide were more toxic to minnows than comparable solutions of cyanide alone (66). The toxicity of zinc salts to sticklebacks *(Gasterosteus aculeatus)* maintained in soft water was reduced by the addition of either calcium chloride or calcium carbonate (66).

TABLE 8.

Toxic Effects of Zinc Chloride to Freshwater and Marine Organisms

Concentration (mg/1)	Duration of Exposure (hr)	Species	Effects Produced	Reference
FRESHWATER				
4.3	96	*Nitzschia linearis*	LC_{50}	Becker and Thatcher, 1973 (61)
0.79-1.27	96	*Physa heterostropha*	LC_{50}	Ibid
1.5	64	*Daphnia magna*	Minimum lethal concentration	Anderson, 1948 (61a)
0.3	96	*Lebistes reticulatus* (common guppy)	Minimum lethal concentration	Chen, et al., 1969 (62)
20-22	48	*Tilapia mossambica*	LC_{100}	Sreenivasan and Raj, 1963 (63)
10-15	48	*Tilapia mossambica*	LC_{50}	Ibid
5 and 2 mg/1 dissolved oxygen	96	*Lepomis macrochirus* (bluegill sunfish)	LC_{50}	Cairns and Scheier, 1957 (64)
8 and 8-9 mg/1 dissolved oxygen	96	*Lepomis macrochirus*	LC_{50}	Ibid
1	24	*Cyprinus carpio*	Killed	McKee and Wolf, 1963 (66)
17.1	1	minnows (species not available)	No effect	Ibid
0.14	50	*Anguilla rostrata* (juvenile eel)	Maximum tolerated concentration	Ibid
0.65 (as zinc)	12	*Anguilla rostrata*	Killed	Ibid
0.17	N.A.	*Etheostoma histrio* (harlequin fish)	LC_{50}	Anon., 1975 (66a)

TABLE 8. (cont.)

Toxic Effects of Zinc Chloride to Freshwater and Marine Organisms

Concentration (mg/l)	Duration of Exposure (hr)	Species	Effects Produced	Reference
157-180	2	*Fundulus heteroclitus* (Mummichog)	Became sluggish	Becker and Thatcher, 1973 (61)
157-180	24-48	*Fundulus heteroclitus*	Killed	Ibid
66	48-192	*Fundulus heteroclitus*	LC_{50}	Ibid
43	192	*Fundulus heteroclitus*	Tolerable concentration	Ibid
5.2	48	*Lepomis macrochirus*	LC_{50}	Ibid
2.86-3.78	96	*Lepomis macrochirus*	LC_{50}	Ibid
7.24	24	*Lepomis macrochirus*	LC_{50}	Ibid
7.24	48	*Lepomis macrochirus*	LC_{50}	Ibid
5.37	96	*Lepomis macrochirus*	LC_{50}	Ibid
<12	336	*Ictalurus nebulosus* (Brown bullhead)	No effects	Ibid
8.0	96	*Brachydanio rerio* (adult)	No effects	Ibid
28.0	48	*Brachydanio rerio* (adults)	LC_{50}	Ibid
105.0	48	*Brachydanio rerio* (eggs)	LC_{50}	Ibid
10.0	48	Minnows (species not reported)	Killed	Ibid

TABLE 8. (cont.)

Toxic Effects of Zinc Chloride to Freshwater and Marine Organisms

Concentration (mg/1)	Duration of Exposure (hr)	Species	Effects Produced	Reference
16.0	20	*Anguilla* sp. (eels)	Killed	Ibid
100	96	Fish (species not reported)	No mortalities	Ibid
200	48	*Fundulus heteroclitus*	Killed in freshwater No mortalities in seawater	Ibid
1000	24	Trout (species not reported)	Killed	Ibid
7.45	96	*Lepomis macrochirus* (small)	LC_{50}	Ibid
7.20	96	*Lepomis macrochirus* (average)	LC_{50}	Ibid
6.91	96	*Lepomis macrochirus* (large)	LC_{50}	Ibid
MARINE				
0.17	42-48	*Mercenaria mercenaria* (hard clam)	LC_{50}	Calabrese and Nelson, 1974 (68)
0.25	42-48	*Mercenaria mercenaria*	Concentration causing 100% mortality	Ibid
0.9-1360	6,18,24	*Dendraster excentricus* (sand dollar	Abnormal cleavage; Abnormal development patterns	Rulon, 1955 (69)

TABLE 8. (cont.)

Toxic Effects of Zinc Chloride to Freshwater and Marine Organisms

Concentration (mg/l)	Duration Exposure (hr)	Species	Effects Produced	Reference
2.5-10 mg/l	17	*Arbacia puntulata* (sea urchin)	Inhibition of gastrulation, persistent fertilization membranes; death-especially at high concentrations; abnormal development	Waterman, 1937 (70)
100 mg/l alternating with sea water	5 minute intervals	*Arbacia punctulata* (sea urchin)	Abnormal development; persistent fertilization membranes	Ibid
0.14-13.6	N.A.	*Paracentrotus lividus* (sea urchin)	Lysis, abnormal and delayed development	Lallier, 1955 (71)

N.A. - Not Available

LC_{50} - median lethal concentration

LC_{100}- lethal concentration at which 100% died

X. EFFECTS ON MICROORGANISMS

Zinc chloride has been shown to reduce survival and have a lethal effect on bacteria. Kiortsis (72) investigated the combined lethal effects of zinc chloride and gamma irradiation on cultures of *Bacillus megaterium* (strain Elstre). Samples of *B. megaterium* cultures were irradiated with gamma rays from a 500 curies cobalt-60 source. The dose rate was about 400 rads/minute given for 5, 15, or 60 minutes (2,000, 6,000 and 24,000 rads, respectively). Another series of samples were treated with 6×10^{-6} or 12×10^{-6} M zinc chloride for 45, 60 or 120 minutes. Finally, another series of samples were exposed to both zinc chloride and gamma irradiation (same doses as in the previously described series). Exposure to 6×10^{-6} M zinc chloride alone for 45, 60 or 120 minutes decreased the percentage survival to 70, 66 or 34 percent, respectively, while 12×10^{-6} M zinc chloride decreased survival to 45, 40 or 20 percent, respectively. Gamma irradiation alone decreased survival in a dose-related manner. A 72, 55, and 15 percent decrease was evident with 2,000, 6,000 and 24,000 rads, respectively. Combination of zinc treatment and gamma irradiation caused even greater reductions in survival. At the lower concentration (6×10^{-6} M), irradiation with 2,000, 6,000 and 24,000 rads decreased the survival percentages to 30, 17, or 3.7 percent, respectively. While with 12×10^{-6} M zinc chloride and the same irradiation doses, survival was reduced to 11, 6 or 0.5 percent, respectively. The author suggested that the synergistic effect of zinc chloride and gamma irradiation could be attributed to the combination of two "inactivating agents" which affect cell growth and cell multiplication (72).

XI. EFFECTS ON PLANTS

Zinc chloride is one of several inorganic compounds which have been used as herbicides (73). Leaf immersion into zinc chloride caused leaf injury in corn and tomato plants, and inhibited growth of cauliflower, lettuce, and carrot explants. Zinc is present in most plants in amounts varying from 1 to 10 mg/kg and up to 140 mg/kg in cereals (66). Though zinc is required for normal plant growth, excess zinc from water, soils or air contamination can accumulate in plants and have toxic effects.

The effects of leaf immersion into a solution of zinc chloride was also described by King (73). Recently emerged leaves of 15-25 day old corn (*Zea mays L.* var. Early Golden Orange Dent) seedlings were immersed into 100 ml of 1% zinc chloride and observed for signs of visible injury. In the same manner, the terminal leaflets of a leaf one-half way up the axis of young potted tomato plants (*Lycopersicon esculentum* Mill. var. Bonny Best) were also immersed in a zinc chloride solution. The types of injuries observed were not reported. After 24 hours, injury was evident over approximately 80% of the immersed corn leaf and covered the entire leaf within 48 hours. After 7 days, the entire plant was involved. The zinc chloride solution was not as toxic to tomato plants, injury being evident over approximately 30, 65, and 75% of the leaf area in 24 and 48 hours, or 7 days, respectively (73).

Immersion of explants of cauliflower inflorescence stems, lettuce stems, the secondary phloem of carrot roots, and potato tuber medullae in 0.0, 0.5, 5.0, or 50.0 mg/1 zinc chloride solutions for a 20-day period had varying effects (74). The growth of lettuce cultures was inhibited but the results were erratic, especially at 50.0 mg/1. Carrots were generally tolerant though some growth inhibition was evident at 50.0 mg/1. Cauliflower does not tolerate zinc in excess of 0.5 mg/1. The zinc treatment had no effect on potato explant cultures (74).

Zinc content in soils can vary from near zero to more than 100 mg/kg. Nitrogen content of peas increased with the addition of 2 mg of zinc per kg dry soil (66). Nutrient solution containing about 0.1 mg/1 of zinc was required for normal growth of 2 species of pine seedlings, and 2 mg/1 zinc in water suppressed root fungus in watercress without harming plants (66). Delayed germination and severely retarded growth in cress and mustard seeds was observed over an 18-day observation period with plants grown in 54-436 mg/1 zinc in a nutrient solution. Concentrations of 3 mg/1 zinc in nutrient solutions were toxic to orange and mandarin seedlings; 5 mg/1 was toxic to flax and 10 mg/1 was toxic to water hyacinths. Zinc sulfate at concentrations of 25-100 mg/1 was toxic to oats (66). The yield of grass was considerably reduced by 6.5 mg/g zinc in soils. A general toxic limit for zinc in plant dry matter is estimated at 400-500 µg/g (45). Iron deficiency was produced in sugar beets and oats at 16-20 mg/1 and 2.5 mg/1 zinc, respectively. Peking variety soybeans were killed by 0.4 mg/1 zinc, whereas the Manchu variety was killed at 1.6 mg/1 zinc (66).

XII. PHARMACOKINETICS

The pharmacokinetics of zinc chloride in humans, experimental mammals and livestock will be reviewed in this chapter. Zinc occurs naturally in almost all biological systems. Humans ingest about 10 to 15 mg zinc/day, while while the total zinc content in the body is estimated to be 2 g (75). Absorption, distribution, retention, and excretion studies in humans and other animals, therefore, require use of radioactive zinc (usually as ^{65}zinc chloride).

A. HUMANS

Zinc chloride exposure in the field, via inhalation, skin contact, and possibly ingestion (dirty hands, contaminated food, cigarette smoking, etc.) may, in some cases, lead to absorption of zinc into the blood stream. Although information on pulmonary and skin absorption of zinc in humans was not available, there are data on the fate of zinc chloride once it has entered the bloodstream. In the following section, reports concerning intravenous injections of radioactive zinc chloride (^{65}zinc chloride), as well as oral administration of the compound, are reviewed (76-78).

1. Absorption, Distribution, and Retention

Zinc chloride smoke particles are inhaled into the lungs, and the caustic properties of the compound are responsible for respiratory irritation varying from dry throat to bronchopneumonia (6,7,12-20). MacAulay and Mant (18) reported that 6.73 mg zinc/100 g of tissue were present in the left lung of an individual who died 11 days after a 4 minute exposure to highly concentrated zinc chloride smoke. No studies were available, however, in which the absorption of zinc from pulmonary tissue into the blood was explored.

Following a single intravenous administration of a tracer dose of ^{65}zinc chloride in 8 patients with various malignancies, the levels of radiozinc in plasma and whole blood were determined (22,79). The ^{65}zinc levels in whole blood and plasma were initially similar and decreased rapidly. Half an hour after the injection, 90% of the administered dose had left the vascular space, and at one hour, only about 4% of the dose remained in the whole blood. After this time, the concentration of ^{65}zinc in the plasma began to decrease, while the concentration in whole blood continued to increase. At 24 hours, the level of ^{65}zinc in whole blood was about four times higher than in plasma. The concentration in whole blood started to decrease 10 days after the injection of radiozinc. At 40 days, the whole blood level of radiozinc was still three times higher than the plasma level, and at 75 days, it was twice as high as the plasma levels. The uptake of ^{65}zinc in the whole blood and plasma in man 4 hours and 5 days after intravenous injection of ^{65}zinc chloride is shown in Table 9.

In another experiment, fourteen pre-terminal patients having various malignancies were given 100 microcuries of radioactive ^{65}zinc chloride (77). The radioisotope was administered as an intravenous infusion in a 250-ml volume of isotonic solution. The distribution of the radiozinc was studied in the liver, pancreas, spleen, prostate, seminal vesicles, lung, bladder and skeletal muscle at autopsy, which occurred between 1 and 174 days after the

TABLE 9.

^{65}Zinc Uptake in Whole Blood and Plasma in Man after Intravenous Administration of ^{65}Zinc Chloride

Patient	Age years	Sex	^{65}Zinc, Percent Dose/Total Volume					
			Whole Blood		Plasma		Whole Blood/Plasma Index	
			4 Hours	5 Days	4 Hours	5 Days	4 Hours	5 Days
1	58	F	8.6	6.1	2.7	1.0	3.2	6.1
2	73	M	2.2	6.3	2.2	1.3	1.0	4.9
3	56	M	3.2	7.6	2.0	1.7	1.6	4.5
4	65	M	4.5	8.2	2.4	0.8	1.9	10.3
5	70	M	2.5	5.0	1.3	0.8	1.9	6.3
6	50	F	3.3	11.5	2.6	1.3	1.3	8.9
7	58	F	-	4.7	-	1.0	-	4.7
8	72	F	-	4.7	-	0.9	-	5.2

Ref.: Prasad, 1966 (22)

infusion. The maximum uptake of the radioisotope was as follows: skeletal muscle 92%, liver 65%, spleen 6%, lung 5%, pancreas 2.7%, and prostate 1%. A small percentage of the administered dose was distributed in the seminal vesicles and bladder. The maximum level of the radiozinc in the liver was found on about the seventh day after dosing, declining slowly thereafter. As late as 174 days after administration, 3.8% of the dose was still present in the liver. The biological half-life of ^{65}zinc in the liver of humans was estimated to be about 75 days. A more rapid turnover of the administered dose occurred in the pancreas. In this organ, maximum concentration was attained by the second day; within a week, the level of the tagged metal had fallen by two-thirds, and by 81 days, less than one-tenth remained. The maximum ^{65}zinc concentration in the spleen occurred on the third day. For the spleen, as well as those organs having even lower levels of the radioisotope (seminal vesicles, lung, and bladder), no temporal relationship could be discerned (77).

Tissue distribution studies were conducted on 11 patients with metastatic neoplastic disease, ranging in age from 32 to 90 years. A single tracer dose of ^{65}zinc as the chloride was injected intravenously. The tissue samples were obtained at autopsy at time intervals ranging from 1 to 71 days after the injection. Table 10 shows the distribution of ^{65}zinc in various tissues at these time intervals (79).

Absorption studies in humans after oral administration of tracer doses of ^{65}zinc chloride have shown that ^{65}zinc entered the blood stream rapidly from the gastrointestinal tract and reached a peak in the plasma by the fourth hour after the ingestion of the dose (80). The ^{65}zinc level in whole blood was initially lower than the plasma level. Similar to the observations made following the intravenous injection of ^{65}zinc chloride, the level of the radioisotope in whole blood increased with time, so that the ^{65}zinc concentration was distinctly higher in whole blood than in plasma at twenty-four hours. Five days after the ingestion of ^{65}zinc, the ratio of radioisotope in whole blood/plasma ranged from about 2-5, but was lower than that following the intravenous administration (80).

Four human subjects (ages 29-48 yrs) were given a single oral dose of ^{65}zinc chloride (0.6-1.0 microcuries). The average biological half-life of the administered dose of ^{65}zinc was 154 days with a range of 149-161 days (76).

2. Excretion

Following the intravenous administration of ^{65}zinc chloride, the main pathway of excretion of this radioisotope in humans was via the intestine. In 30 days, a total of about 18% of the intravenously administered dose was excreted in the feces, while the total excretion of the radiozinc in urine was less than 1% of the dose (22).

The major portion of ingested radioactive zinc (as $^{65}Zn\ Cl_2$) was excreted in the feces; the amounts varied from 19% to 76% of the administered dose in 15 days. The urinary excretion was low and ranged from 0.7% to 2.1% during 15 days (22).

Studies on zinc excretion in persons exposed to zinc chloride smoke have not been reported in the literature.

TABLE 10.

Tissue Distribution of ^{65}Zinc in Humans* at Different Intervals after a Single Intravenous Injection of ^{65}Zinc Chloride (100 Microcuries)

Tissue	^{65}Zinc (% dose x 10^3/g wet tissue)			
	Days after Injection			
	1	13	17	71
Liver	61	43	20	15
Kidney	40	10	14	4
Spleen	12	5	3	2
Lung	4	3	-	1
Intestine	4	3	2	-
Stomach	1	4	2	-
Skeletal muscle	1	1	1	2
Pancreas	11	3	3	1
Adrenal	9	5	2	2
Thyroid	-	5	4	-
Prostate	2	4	6	3

*Data obtained from different patients upon autopsy.
Ref.: Spencer et al., 1965 (79).

B. EXPERIMENTAL ANIMALS

The absorption, distribution, and excretion of ^{65}zinc by experimental animals following cutaneous application, oral administration, and intravenous injection have been investigated.

1. Absorption, Distribution, and Retention

Zinc chloride is poorly absorbed through the skin as shown by percutaneous application of radioactive zinc chloride to guinea pigs. Measurements of disappearance of zinc from 0.08-4.87 M aqueous ^{65}zinc chloride solutions (volume of application not specified) showed that less than 1% ^{65}zinc was absorbed in 5 hours (81).

There are contradictory reports on the degree of absorption of ^{65}zinc chloride in rats after oral administration. Feaster et al. (82) reported that after feeding a single tracer dose of ^{65}zinc chloride to 44 adult female rats, only 5% of the administered dose was absorbed after 24 hours. In contrast to this report, a more recent report by Methfessel and Spencer (83) shows that the intestinal absorption of ^{65}zinc in rats was 25% within 30 minutes after the intubation of ^{65}zinc chloride. This level of ^{65}zinc absorption was maintained over the next 7.5 hours. Similar intestinal absorption rates were observed when $^{65}ZnCl_2$ was instilled into *in vivo* ligated sacs formed from the duodenal portion of the small intestine. The absorption of ^{65}zinc was significantly greater from the duodenum (27%) than from more distal portions of the small intestine. The absorption of ^{65}zinc was slightly greater from the midjejunum (11%) than from the ileum (8%) but the difference was not statistically significant. Only minimal amounts of ^{65}zinc were absorbed from the stomach (0.2%), the cecum, and the colon (2.2%) (83).

The distribution of radiozinc in 44 female rats after a single tracer dose of ^{65}zinc chloride (given orally) was studied by Feaster et al. (54). The rats were killed 4 days after the administration of the isotope. The kidney, liver and pancreas contained the highest concentrations of activity. Relatively little accumulation was noted for muscle, hide and hair, and bones. The distribution of retained ^{65}zinc in selected tissues of rats 4 days after the administration of the doses is given in Table 11.

The distribution studies of radioactive zinc chloride in the rabbits have shown similar results (84). A group of 18 female rabbits were given ^{69m}zinc chloride in 0.1 N hydrochloric acid by ear-vein injection. The greatest accumulation of ^{69m}zinc per gram of tissue was found alternately in the pancreas, liver and intestines between 2 and 20 hours after the injection. Heart, lung and muscle showed lesser concentrations of the ^{69m}Zn, while fat showed the lowest concentrations. The distribution of ^{69m}zinc in various tissues of the rabbits between 2 and 20 hours after the injection is given in Table 12.

Mice were given 0.33-1.6 µg of radioactive ^{65}zinc chloride intravenously. The injected radiozinc rapidly disappeared from the plasma. The highest concentration of ^{65}zinc was found in the liver. The distribution of ^{65}zinc in various tissues of the mice between 45 minutes and 170 hours after injection is summarized in Table 13 (78).

TABLE 11.

Distribution of Retained ^{65}Zinc in Selected Tissues of the Adult Rat 4 days after the Oral Administration of a Single Tracer Dose of ^{65}Zinc Chloride

	Percentage of retained dose per gram of fresh tissue						
Blood	Muscle	Pancreas	Liver	Kidney	Spleen	Hide & Hair	Femur
Less than 0.04%	14.3	36.0	39.0	67.0	29.0	7.0	21.0

Calculations based on 7% dose retention

Ref.: Feaster et al., 1955 (82)

TABLE 12.

Distribution of ^{69m}Zinc in the Tissues of Rabbits (percent dose per gram in tissue) after a Single Intravenous Injection of ^{69m}Zinc Chloride

	Time after Injection (hours)					
Tissue	2	4	8	12	16	20
Liver	13	14	13	10	8	4
Pancreas	14	10	3	12	7.5	3.9
Kidney	12	7.6	10	10	6.7	3.1
Spleen	10.4	5.8	8.2	8.8	5.2	2.3
Eye	12	0.4	0.5	0.3	0.2	0.5
Lung	4.9	3.5	3.5	3.9	1.8	2.2
Muscle	0.8	0.7	0.7	0.6	0.3	0.4
Fat	0.6	0.4	0.5	0.5	0.2	0.3
Intestine	13.4	6.2	11.2	9.7	7.0	4.5
Heart	2.5	2.8	4.3	4.6	3.1	1.9

Ref.: Lorber et al., 1970 (84)

TABLE 13.

Distribution of ^{65}Zinc (% dose) in Various Tissues of the Mice[a] after Intravenous Injection of ^{65}Zinc Chloride

Tissue	Time after Injection					
	45 minutes	2 hours	8 hours	26 hours	72 hours	170 hours
Pancreas	2.0	1.7	0.93	0.99	0.52	0.44
Liver	24	25	17	11	6.7	3.3
Kidneys	6.5	5.2	3.0	1.7	0.98	0.50
Stomach	0.83	1.1	1.0	0.99	0.59	0.37
Small intestine	4.5	5.8	8.4	3.8	2.2	0.96
Colon	1.6	2.4	3.8	2.0	1.1	0.83
Heart	0.38	0.54	0.44	0.48	0.29	0.14
Adrenals	0.04	0.04	0.026	0.048	0.021	0.011
Thymus	0.064	0.098	0.079	0.16	0.084	0.038
Brain	0.32	0.38	0.55	0.56	0.77	0.64
Lungs	0.98	1.1	0.97	0.72	0.46	0.26
Spleen	0.84	1.3	1.9	0.73	0.37	0.14
Lymph nodes	0.40	0.42	0.52	0.38	0.38	0.12

Ref.: Sheline et al., 1943a (78)

[a]The mice weighed 17-23 g. Each animal received 0.33-1.6 μg of ^{65}zinc chloride. Each value is the average of three to seven separate analyses on as many animals.

The distribution of zinc chloride in various organs of dogs was studied by intravenous injection of radioactive ^{65}zinc chloride (78). The dogs were given intravenous injections of 6.5-13 µg of ^{65}zinc chloride. Injected radiozinc rapidly disappeared from the plasma. Measurable amounts of ^{65}zinc were no longer detectable in the plasma 10 hours after the injection. The distribution of radiozinc in other tissues was similar to that found in mice, as shown in Table 14.

2. Excretion

The excretion of intravenously injected radiozinc via the urine and feces of two dogs was investigated over a 15-day period following the administration of 5.7 or 6.5 µg of labeled ^{65}zinc chloride. About 25% of the administered dose was found in the feces at the end of 12 to 14 days. In 15 days, the dogs had eliminated 1.2-4.7% of the injected ^{65}zinc in the urine (85).

Mice injected intravenously with 0.33 µg of labeled ^{65}zinc chloride excreted over 50% of the administered dose in the feces in 170 hours. A total of 2% of the radiozinc was eliminated in the urine at the end of this period (85).

C. LIVESTOCK

Several studies on the pharmacokinetics of ^{65}zinc chloride in ruminants, including swine, sheep, and cattle, have been reported in the literature.

1. Absorption, Distribution and Retention

Zinc metabolism has been studied in swine. Four groups of 4 pigs each (mixed breed, 22-39 kg) were given intravenous injections of ^{65}zinc (as ^{65}zinc chloride). Over 90% of the ^{65}zinc in the blood disappeared within one hour. A corresponding amount, however, was not excreted, suggesting that ^{65}zinc had been removed from the circulating blood by the tissues. By the second and third days after administration, a net uptake by the packed cell fraction of whole blood occurred, followed by a marked decrease after the third day (86).

Arora (87) studied the uptake of ^{65}zinc by the rumen tissues of Rambouillet X Hampshire lambs (9 months-old; 30 kg) following intravenous injection of ^{65}zinc (as ^{65}zinc chloride) and 48 mg of stable zinc (as zinc chloride). The maximum of ^{65}zinc by the rumen tissue occurred 12 hours after injection. The rumen concentration of ^{65}zinc was greater than that of the blood.

Another 12 lambs were given single oral doses of ^{65}zinc chloride in distilled water and 48 mg of stable zinc (as zinc chloride) which were administered in a gelatin capsule. The lambs were fed a low zinc diet prior to dosing. The highest concentration of ^{65}zinc per kilogram tissue was evident 48 hours after administration (87).

In a follow-up study, 5 lambs (35 kg) were kept on a low zinc diet for 32 days before oral administration of ^{65}zinc (as ^{65}zinc chloride) and 48 mg stable zinc (as zinc chloride). The animals were sacrificed 48 hours after dosing. A comparison of the ^{65}zinc distribution in different parts of the

TABLE 14.

Distribution of ^{65}Zinc (% dose) in Tissues of Dogs After Intravenous Injection of Labeled ^{65}Zinc Chloride

Tissue	Time after Injection (Hours)				
	3	8	24	94	170
Whole blood	3.2	2.7	1.9	4.2	4.1
Pancreas	2.3	3.1	1.2	2.0	0.69
Liver	38	34	33	11	3.5
Kidneys	3.2	3.9	2.5	1.3	0.90
Stomach	0.88	1.3	0.93	1.2	0.81
Small intestine	5.2	10	4.5	4.1	2.8
Colon & cecum	0.81	1.1	1.2	1.4	1.0
Skeletal muscle	9.5	9.6	13	25	36
Heart	0.58	1.1	0.70	1.1	0.98
Thyroids	0.017	0.018	0.017	0.014	0.0052
Adrenals	0.027	0.054	0.038	0.025	0.014
Pituitary	0.12	0.0061	0.0021	0.0020	0.0020
Brain	0.067	0.36	0.38	0.68	0.62
Lungs	0.63	0.73	0.79	1.1	0.71
Spleen	0.37	0.93	0.72	0.60	0.31
Intestinal lymph nodes	0.07	0.076	0.061	0.048	0.064
Peripheral lymph nodes	0.24	0.27	0.54	0.20	0.32

Ref.: Sheline et al., 1943a (78)

alimentary tract is given in Table 15. The concentration of ^{65}zinc per kilogram of rumen tissue was significantly ($p < 0.01$) higher than abomasal, duodenal, and large intestine levels, indicating that the rumen tissue absorbed a significant amount of zinc (87).

Neathery et al. (88) fed 3 uncastrated male Holstein calves (67-days-old; 65.5 kg) ^{65}zinc (as ^{65}zinc chloride) in a single dose via gelatin capsules. The calves were maintained on a zinc diet (2.7 mg/kg zinc) for 7 days prior to dosing and were sacrificed 7 days after dosing. The net ^{65}zinc absorption was 62% of the treatment dose. ^{65}Zinc concentrations were highest in the liver, followed by the spleen, kidney, heart, small intestine, duodenum and lung (Table 16).

In a similar study, 9 uncastrated male Holstein calves (120-days-old; 114 kg) were fed diets containing 38 (control), 238, and 638 mg/kg zinc (as zinc oxide) for 7 days before being given a single intravenous dose of ^{65}zinc (as ^{65}zinc chloride) (89). The calves were maintained on their respective diets for 14 more days and were then sacrificed. Increasing dietary zinc from 38 to 238 mg/kg significantly ($p < 0.01$) decreased the ^{65}zinc content of the heart, testicle, rumen wall and fundic abomasum. Differences for other organs were not statistically significant. When the zinc content of the diet was increased from 238 to 638 mg/kg, significant ($p < 0.01$) increases in the ^{65}zinc content of the pancreas, liver, kidney, tibial shaft, tibial joint, duodenum, and small intestine resulted. However, the ^{65}zinc content of testicle, heart, rumen wall and fundic abomasum decreased (Table 17) (89).

The ^{65}zinc content of whole blood was not affected by dietary zinc levels. However, ^{65}zinc concentration of blood serum was significantly ($p > 0.01$) higher 24 hours after ingestion of a diet containing 638 mg/kg of supplemental zinc as compared to those with 38 and 238 mg/kg. Whole blood and blood serum levels of ^{65}zinc markedly decreased 4 to 24 hours after intravenous dosing with ^{65}zinc followed by a further slower decline. The decline in ^{65}zinc content was slower in whole blood than in serum (89).

2. Excretion

In livestock, zinc is primarily excreted in the feces. Urinary excretion is generally very low.

When pigs were given intravenous injections of ^{65}zinc chloride, as previously described, the ^{65}zinc was primarily excreted as a result of gastrointestinal secretion and fecal excretion. As much as 75-90% of the ^{65}zinc excreted was voided in the feces regardless of diet. Approximately 95.6% of the injected zinc was excreted with a half-time of 100 days and the remaining 4.4% was excreted with a half-time of 3 days. Excretion was also accomplished by pancreatic, biliary, and duodenal secretion which totalled 0.475%, 0.055%, and 0.150% of the administered dose, respectively, over 4 days. A total pancreatic or gall bladder fistula, a fistula of a 40-cm duodenal segment, and ligation of the pancreatic duct did not appreciably reduce fecal excretion of radioactive zinc (86).

The ^{65}zinc fecal excretion rate of 3 Holstein calves following oral administration of ^{65}zinc chloride peaked 2 days after dosing. This increase

TABLE 15.

^{65}Zinc Uptake in the Lamb Alimentary Tract

Organ	Mean ^{65}Zinc Uptake (% dose/kg tissue)
Rumen	4.56
Abomasum	1.14
Duodenum	1.64
Large intestine	1.82

Ref.: Arora, 1969 (87)

TABLE 16.

Distribution of ^{65}Zinc in the Tissues of Holstein Calves

Organ	^{65}Zinc (% of ^{65}zinc dose/kg fresh tissue)
Liver	3.20 ± 0.35
Spleen	2.51 ± 0.33
Kidney	2.24 ± 0.29
Heart	2.00 ± 0.21
Small intestine	1.95 ± 0.18
Duodenum	1.89 ± 0.24
Lung	1.49 ± 0.14

Ref.: Neathery et al., 1972 (88)

TABLE 17.

Distribution of Intravenously Injected ^{65}Zinc in the Tissues of Calves Fed Diets Containing Various Levels of Zinc

Tissue	% of dose/kg fresh tissue		
	Practical Diet plus 38 mg/kg	Practical Diet plus 238 mg/kg	Practical Diet plus 638 mg/kg
Pancreas	0.71	0.86	5.89
Liver	1.36	0.53	3.92
Kidney	0.76	0.72	3.50
Heart	0.86	0.49	0.35
Testicle	0.56	0.38	0.26
Muscle	0.53	0.50	0.40
Rib	1.18	1.07	1.73
Tibial joint	0.47	0.58	0.84
Tibial shaft	0.42	0.45	0.71
Rumen wall	1.17	0.66	0.41
Abomasum (pyloric)	0.54	0.45	0.35
Abomasum (fundic)	0.82	0.55	0.38
Duodenum[a]	0.64	0.59	0.92
Small intestine[b]	0.67	0.55	0.84
Small intestine[c]	0.74	0.60	0.62

[a] first 1.83 m of small intestine

[b] second 1.83 m

[c] 3.6 m from the center of the remaining intestine

Ref.: Miller et al., 1971 (89)

was followed by a sharp decrease through the fourth day and by a slower decrease through day 7. ^{65}Zinc excretion averaged 38% of the administered dose over the 7-day collection period (88).

Urinary zinc excretion levels are relatively low over a short period (i.e., 2 weeks). Fecal excretion, as discussed earlier, is a good estimate of total excretion. Calves fed diets with 238 and 638 mg/kg of supplemental zinc and given intravenous injections of ^{65}zinc, excreted significantly ($p < .01$) more zinc in their feces than control calves (38 mg/kg dietary zinc). The fecal ^{65}zinc excretion rate reached its peak 2 days after dosing followed by a slow decline. Average daily fecal ^{65}zinc excretion after 14 days was 32% of the peak daily rate. The supplemental zinc (238 and 638 mg/kg) in the diets increased the endogenous ^{65}zinc excretion by 30% (89).

XIII. UPTAKE AND DISTRIBUTION IN AQUATIC ORGANISMS

Zinc ion is found in seawater at concentrations of 15 µg/1 (70). The uptake and distribution of ^{65}zinc by marine fish, molluscs, and echinoderms have been reported. However, studies in freshwater species were not located in the literature.

Kameda et al. (90) studied the uptake and concentration factor of ^{65}zinc (as ^{65}zinc choride) in marine fish, molluscs and sea urchins. The organisms were kept in seawater to which 12, 50, 150 or 1050 µg Zn/1 (as $ZnCl_2$), containing ^{65}zinc, were added. Uptake and concentration factors for ^{65}zinc in the tissues of each species were measured over a 40-day period. The concentration factor was determined as the ratio of the concentration of ^{65}zinc in the organism to that of the environmental water.

Marine goby *(Chasmichthys gulosus)* and filefish *(Rudarius ercodes)* were chosen as representative fish species. ^{65}Zinc largely accumulated in the digestive tract, gills, and viscera of both species with lower concentrations in the vertebra and muscles. The concentration factors of different tissues are given in Table 18 (90).

^{65}Zinc concentration in the short-necked clam (*Tapes japonica*) was highest in the gills and mantle. It continued to accumulate in the gills, adductor muscle, and mantle even after 30 days. In the mussel, *Mytilus edulis,* ^{65}zinc content was highest in the adductor muscle, shell, and visceral mass and had reached a constant level within 20 days. A comparison of the concentration factors of these 2 species is given in Table 19 (90).

^{65}Zinc concentrations in the sea urchin, *Strongylocentrotus pulcherrimus* were highest in the digestive tract. It was also highest when compared to the organs and tissues of the fish and mollusk species. Accumulation was lower in the test, gonads, and Aristotle's lantern. Concentration factors for the tissues of *S. pulcherrimus* are given in Table 20 (90).

TABLE 18.

Concentration Factors of ^{65}Zinc in Marine Fish Over a 40-Day Experimental Period

Tissue	Concentration Factor	
	C. gulosus	*R. ercodes*
Digestive tract	15	20
Gills	10*	15
Visceral mass	8	8
Vertebra	5*	7
Muscle	3*	4
Head, Fin, Skin	3	5

Concentration Factor - the ratio of the concentration of ^{65}zinc in the organism to that in the environmental water.

*Equilibrium was not reached. Therefore the concentration factors should be higher than these values.

Ref.: Kameda et al., 1968 (90)

TABLE 19.

Concentration Factors of ^{65}Zinc in Two Species of Marine Mollusca over a 40-Day Experimental Period

Tissue	Concentration Factor	
	T. japonica	*M. edulis*
Gills	80*	70
Mantle	60*	40
Adductor muscle	50*	300
Visceral mass	50	350
Shell	50	400

Concentration Factor - the ratio of the concentration of ^{65}zinc in the organism to that in the environmental water.

*Equilibrium was not reached. Therefore the concentration factors should be higher than these values.

Ref.: Kameda et al., 1968 (90)

TABLE 20.

Concentration Factors of ^{65}Zinc in *Strongylocentrotus pulcherrimus* over a 40-Day Experimental Period

Tissue	Concentration Factor
Digestive tract	500*
Gonad	40
Test	40
Aristotle's lantern	20

Concentration Factor - the ratio of the concentration of ^{65}zinc in the organism to that in the environmental water.

*Equilibrium was not reached. Therefore the concentration factor should be higher than these values.

Ref.: Kameda et al., 1968 (90)

XIV. BIOACCUMULATION

Zinc occurs naturally in water and soil. Zinc chloride smoke screens disperse zinc into the environment, as described in Section XV, Occurrence, Dispersion, and Fate in the Environment. From all these sources, zinc can accumulate in plants, wildlife, domestic animals, and aquatic organisms which are subsequently utilized by humans. Possible routes for the accumulation of zinc in the food chain are diagrammed in Figure 3.

A. PLANTS

Zinc can accumulate in grasses, forage plants and other vegetation as a result of direct fallout or through absorption from soil. Soils treated with 150 metric tons/ha* of sludge containing 570 mg/kg zinc resulted in 100 µg/g zinc in healthy perennial rye grass (45). In a similar study, annual applications of digested sewage sludge were made on soil for 8 growing seasons (91). Corn plants (*Zea mays*) were continuously planted throughout the experimental period. On a dry weight basis, the sludge used had an average concentration of 4300 mg/kg zinc. Forty-six percent of the applied zinc was retained in the soil. Zinc content of the leaves and grain increased significantly ($p < 0.01$) with increasing rate of sludge application. Zinc content of leaves increased with each year (significance not reported). However, the zinc content of grain was only about 20% of that found in leaves (91). Application of 20% superphosphate fertilizer containing 129 mg/kg zinc caused zinc accumulation in grains, leaves and legumes but not in roots, squashes, and tomatoes (92).

Radioactive ^{65}zinc has been shown to accumulate in plants (66). Crops irrigated with water from a river 48 kilometers below a nuclear power plant were assayed for ^{65}zinc. The following concentration factors (ratio of zinc in the crops to that in the irrigation water) were observed: pasture grass, 440; black-eyed peas, 2.9; tomatoes, 2.4; okra, 2.1; string bean, 1.5; corn, 0.83 and grapes, 0.47. Plants can concentrate ^{65}zinc depending on the species, stage of growth, plant part, acidity and chemical composition of the nutrient media, temperature, light and soil structure. Accumulation of ^{65}zinc in barley plants has been demonstrated (66).

B. AQUATIC ORGANISMS

Duke (93) studied the possible routes of ^{65}zinc from an experimental estuarine environment to man. The study area was a pond connected to an adjoining estuary by a tile pipe. The test organisms monitored included:

Marsh grass *(Spartina alterniflora)*
American oysters *(Crasastrea virginica)*
Hard clams *(Mercenaria mercenaria)*
Scallops *(Aequipecten irradians)*
Blue crabs *(Callinectes sapidus)*
Mud crabs *(Panopeus herbstii)*
Atlantic croakers *(Micropogon indulctus)*
Mummichogs *(Fundulus heteroclitus)*

*ha-hectare

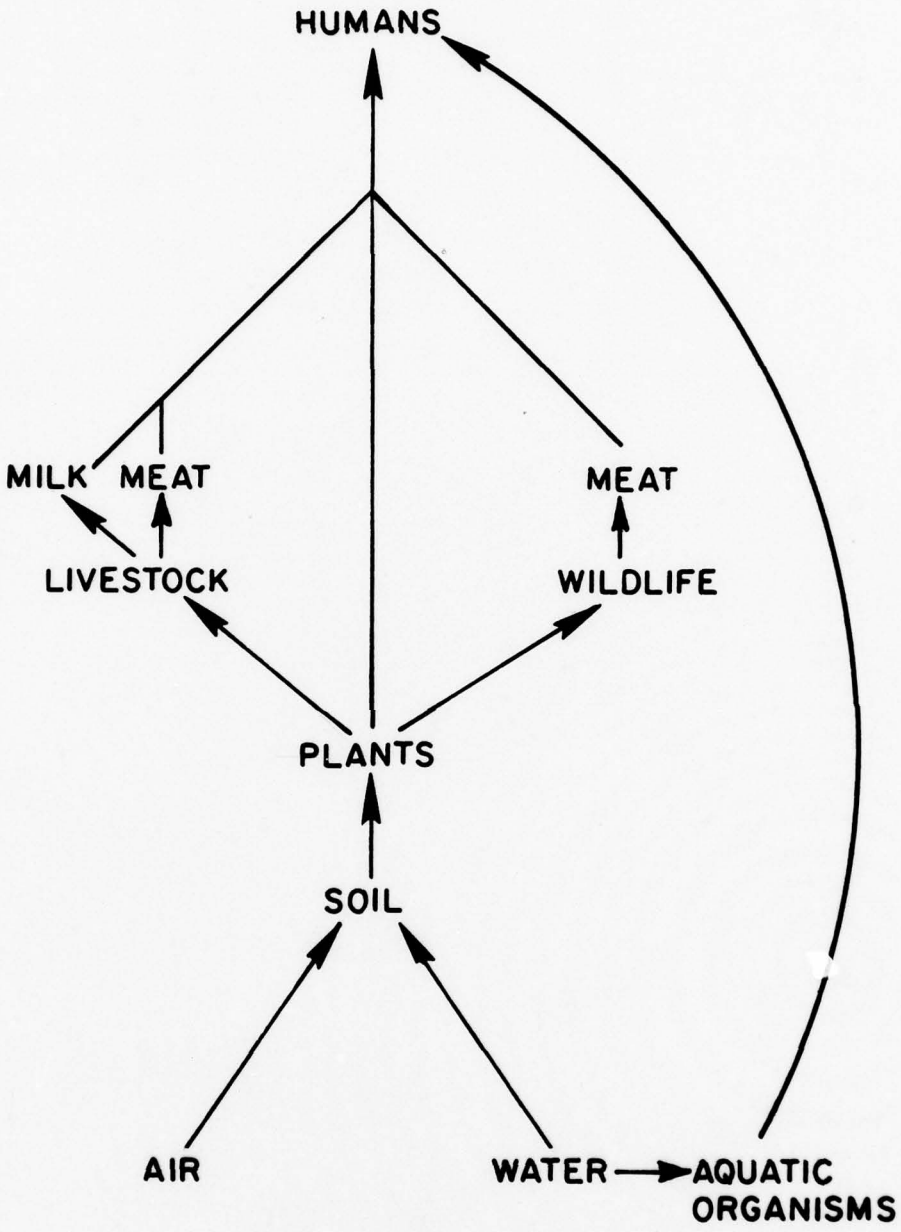


Figure 3. A theoretical model for the concentration of zinc in the food chain.

Ten millicuries of ^{65}zinc (as ionic zinc) in 0.92 hydrochloric acid were added to the pond by spraying over the surface. Water, biota, and sediment samples were removed periodically for analysis.

The zinc moved rapidly from the water to the sediments to the organisms before being lost through tidal exchange of water with the adjoining estuary. Analysis of the ^{65}zinc remaining in the pond after one day revealed 36% in the sediment, 5% in the biota, and the remainder in the water. The latter was generally associated with suspended material. After 100 days, 99.4% was in the sediments, 0.6% in the biota and none was detectable in the water.

Maximum levels of ^{65}zinc in each organism were reached within 2 days. After 100 days, scallops contained 30% of the maximum level, oysters 60%, and clams 25%. Several components of the pond concentrated the zinc. Scallops, clams, and oysters, which accumulate ^{65}zinc more rapidly than other test organsims, are eaten by man and, thus, demonstrate the routes and quantities reaching man. Oysters and clams accumulated more zinc in edible tissue than scallops. The sediments, however, absorbed the greatest amounts (93).

Less than 1% of the ^{65}zinc introduced into the pond was accumulated by seafood organisms. The accumulation by the biota was affected by loss of zinc^{65} with water in the adjoining estuary and through absorption by the sediments. Variation of pond conditions can vary the movement of the zinc (93).

Zinc is accumulated by some marine species. Marine animals contain zinc in the range of 6 to 1500 mg/kg (67). ^{65}Zinc accumulates in algae, brown algae, marine bacteria, and the soft part of marine invertebrates, especially oyster and clam meat. Oysters and shellfish concentrate ^{65}zinc from their environment, often by a factor of 100,000. A large part of this concentration occurs in the plankton on which oysters feed (66).

C. WILDLIFE AND DOMESTIC ANIMALS

Wildlife and domestic animals accumulate zinc from water, grasses, and forage. Zinc is concentrated in certain mammalian tissues, especially in muscle meats. Livestock grazing on pasture grass irrigated with water containing ^{65}zinc accumulate zinc in their beef, bones, flesh as well as their milk (66).

D. HUMANS

Zinc in milk, meat, shellfish, oysters, clams, grain, and vegetables can become concentrated in man. The adult body contains 30-60 mg zinc which is accumulated over a 45-year period. The infant body contains little or no zinc. Therefore, 0.67-1.3 mg zinc per year must be retained in the body (92).

XV. OCCURRENCE, DISPERSION, AND FATE IN THE ENVIRONMENT

Zinc occurs naturally in ores, in trace amounts in igneous rocks, and in varying concentrations in water, animals, plants, and man. Dispersion of zinc chloride in the environment may arise from zinc chloride smoke screens and from industries. Several factors determine the subsequent movement of zinc and its fate in the environment. These topics will be discussed in this chapter.

A. OCCURRENCE IN THE ENVIRONMENT

Zinc is found as a mineral in earth's crust, usually associated with other base metals such as copper and lead. The principal mineral of zinc is the sulfide (Sphalerite). Besides its occurrence in ores, zinc is widely distributed in igneous rocks in trace amounts. Igneous rocks make up 95% of the earth's crust to a depth of 10 miles. Their zinc content is believed to be near 0.01%. In the weathering of rocks, zinc passes into solution and is subsequently precipitated in various forms such as carbonate, silicate, or phosphate (1).

In samples from U.S. waterways, the maximum observed value is 1.2 mg/l with a mean value of 0.064 mg/l. The highest mean value, 205 µg/l, for dissolved zinc has been found in the Lake Erie basin, whereas the lowest mean zinc value, 16 µg/l, has been found in the California basin (67).

In zinc-mining areas, zinc has been found in natural waters in concentrations as high as 50 mg/l but, in most surface and ground waters it is present only in trace amounts (66).

The concentrations of zinc to be expected from various natural sources are: earth's crust, 65 mg/kg; seawater, 15 µg/l; man, 33 mg/kg; wild animals, 22-30 mg/kg; sea foods, 18 mg/kg; meats, 31 mg/kg; legumes, 11 mg/kg; roots and leaves, 1-4 mg/kg; fruits 0.5 mg/kg; grains and cereals, 18 mg/kg; nuts, 34 mg/kg; and spices, 33 mg/kg (92).

B. DISPERSION AND ENVIRONMENTAL FATE

Zinc chloride is one of the major constituents of HC smoke. The smoke is used for screening purposes and for fire-fighting exercises (16,17,19). These smoke generating operations would be potential sources for the dispersion of zinc chloride in air, soil, vegetation, and waters. Dispersion of zinc chloride in the environment may also arise from industrial effluents and wastes (60,68). Industries utilizing zinc chloride and which may disperse it in the environment include metallurgy, textiles, wood treatment, oil refining; pharmaceuticals, adhesive, and cement and agricultural chemicals manufacturing (1,4,5,31).

Once in the environment, zinc chloride hydrolyzes to form various ionic species and other products. Thus, under atmospheric conditions zinc chloride forms hydrochloric acid and zinc oxychlorides ($ZnCl_2.nZ_nO$). In water, zinc

chloride is dissociated to zinc ion (Zn^{++}) and chloride ion (Cl^{-}), and forms such species as $Zn(OH)^{+}$, $Zn(OH)^{+3}$, and $Zn(OH)_2$. In very basic solutions zincates, $[Zn(OH)_3^{-}]$ and $[Zn(OH)_4^{--}]$, are formed (94). The distribution of molecular and ionic hydrolysis species of divalent zinc at different pH values is given in Figure 4.

Zinc ion (Zn^{++}) forms insoluble precipitates with carbonate, sulfide, phosphate, and silicate ions. In waters which are highly carbonated, the occurrence of a double salt $Zn_4(OH)_6(CO_3)_2$ has also been reported. The formation of these insoluble products is responsible for the immobilization of zinc in waters and soils (94). The solubility products of some of the insoluble compounds of zinc which are most likely to be present in the environment are as follows (2,95):

Compound		Solubility Product (pKsp)
Zinc carbonate	$ZnCO_3$	10.84
Zinc sulfide	ZnS	25.15
Zinc hydroxide	$Zn(OH)_2$	15.50
Zinc phosphate	$Zn_3(PO_4)_2$	32.04

All soils contain zinc, the levels in most soils ranging between 10-300 mg/kg. Zinc as Zn^{++} is much more mobile under anaerobic than aerobic soil conditions. The movement in acidic soils is faster than in neutral or alkaline soils. In a study of the mobility of zinc in 8 Washington soils, it was found that zinc is retained well in the upper part of 2 cm x 75 cm soil columns when leached with the equivalent of 2 feet of water after applying zinc at a rate of 0.2 g Zn/cm^2. Six of the 8 soils were fine sandy loams; one was a fine sand, and one was a loam. Clay content was low in all the soils. Application of zinc salts to the soils resulted in a high zinc concentration in the upper few centimeters (5-10 cm). Zinc was precipitated at or near the surface in the soil containing calcium carbonate or lime. The same was true for the soils highest in organic matter (94).

Movement of zinc to 30 cm has been observed in an acid soil which had received a surface application of 16.8 metric tons/ha of sewage sludge (96). Practically all of the zinc remained in the surface 20 cm of soil following application of 84 metric tons/ha of sewage sludge for 12 years (94). There are also data showing evidence of movement of zinc below 15 cm in soil after application of 44-166 metric tons/ha of sludge over a 3-year period (97).

Zinc may be retained in soils due to adsorption, forming a zinc-soil complex as well as zinc hydroxide or $Zn(OH)^{+}$ complex ions (94). The zinc species in equilibrium with soil zinc has been found to be Zn^{++} below pH 7.7, and above this pH the neutral species $Zn(OH)_2$ predominates. Figures 5, 6, and 7 compare the solubility of various zinc species in equilibrium with soil zinc.

There are many factors which should be taken into consideration while determining the rate of migration or mobilization of zinc in soils. Before

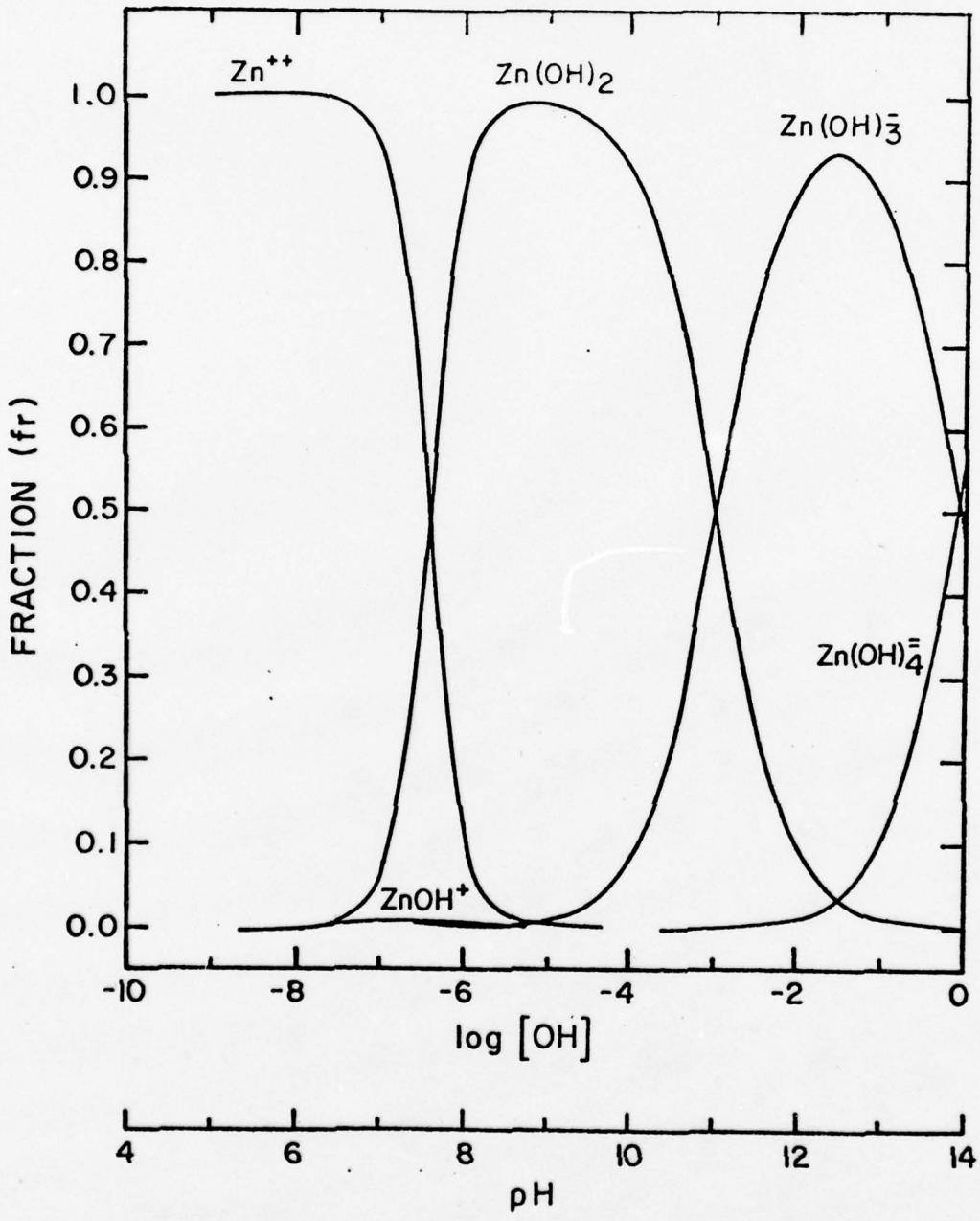


Figure 4. Distribution of molecular and ionic species of divalent Zn at different pH values.

From Fuller, 1977 (94)

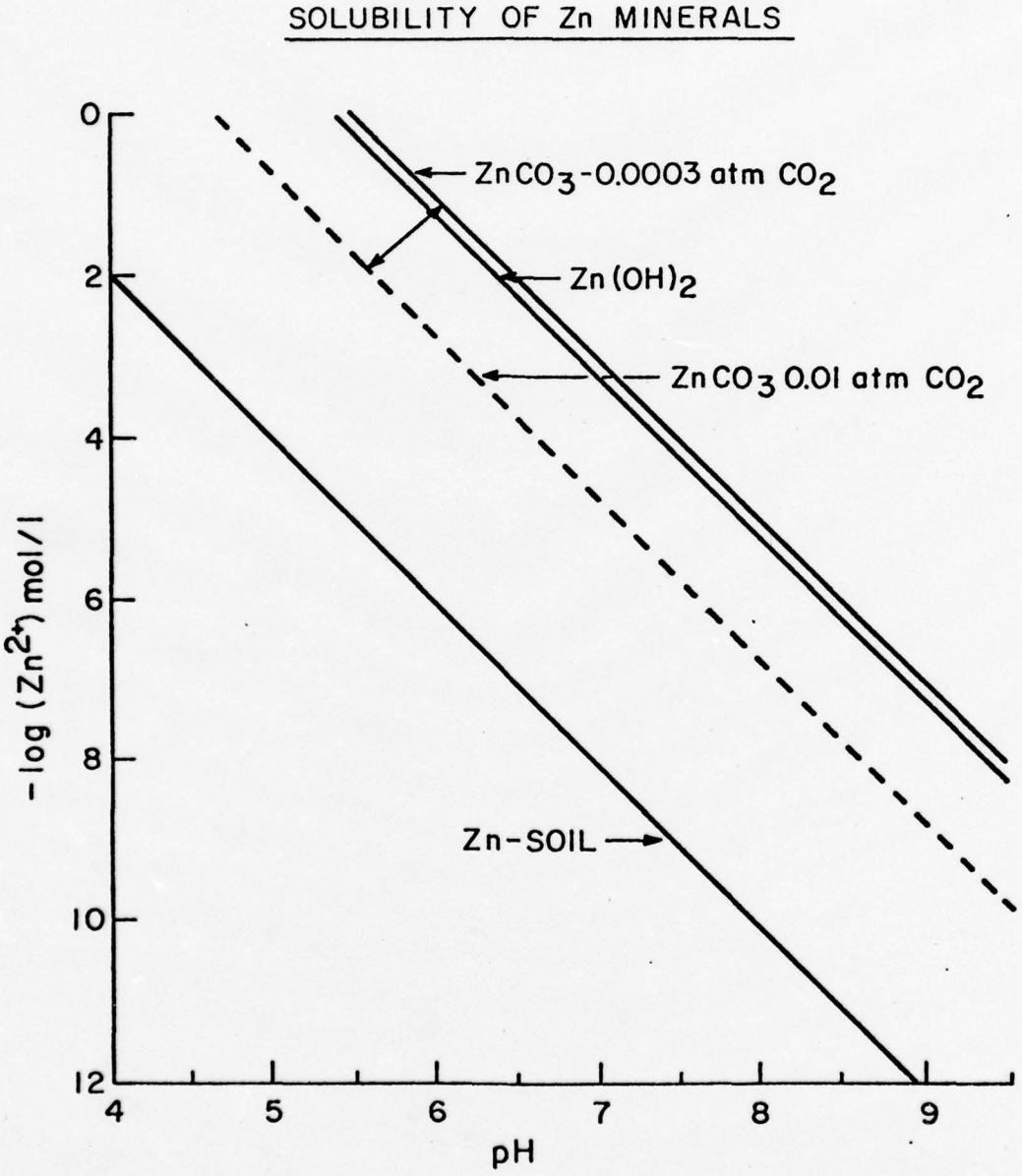


Figure 5. The solubility of various Zn minerals compared to the solubility of Zn in soils.

From Fuller, 1977 (94)

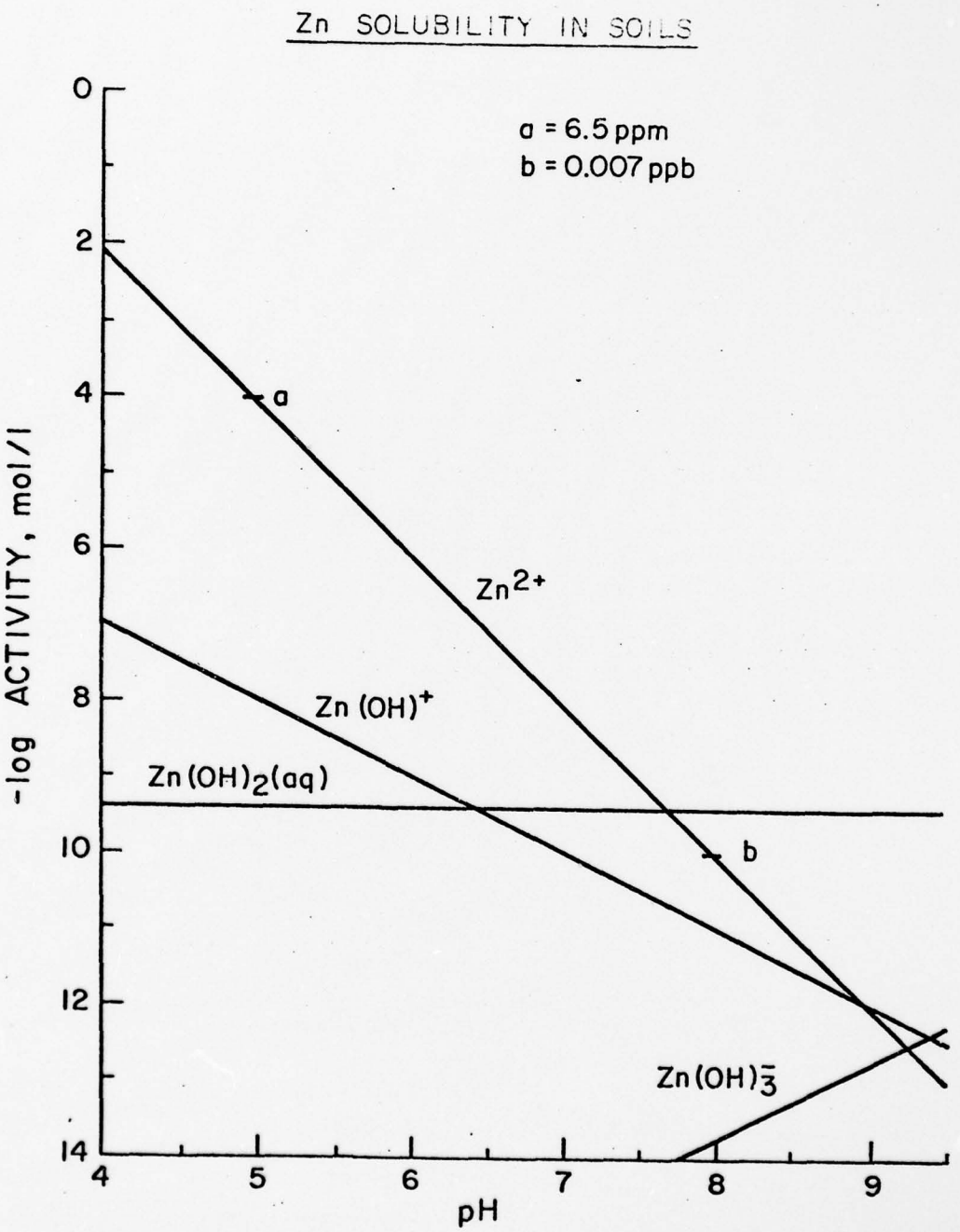


Figure 6. Soluble Zn species in solution in equilibrium with soil Zn.

From Fuller, 1977 (94)

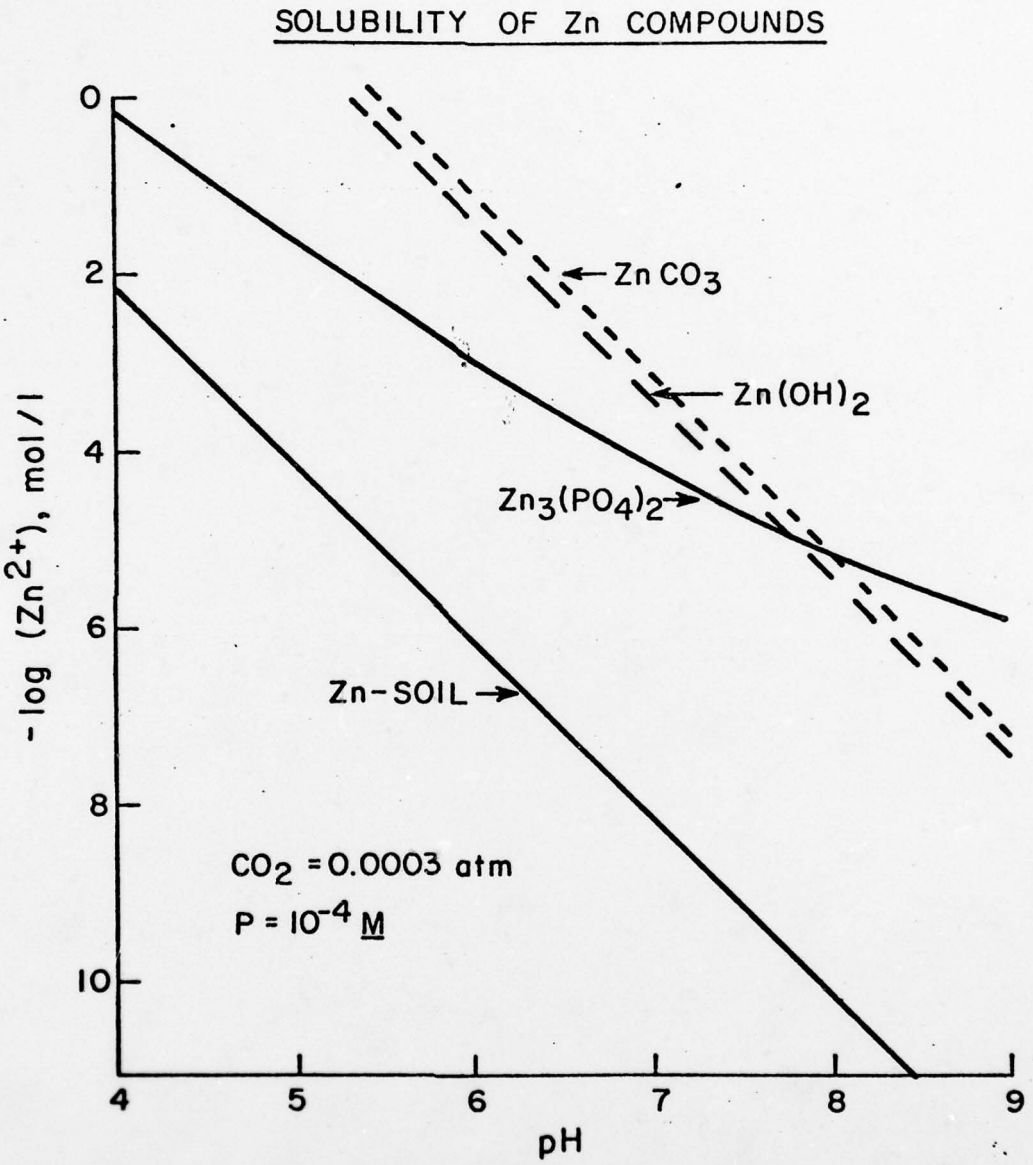


Figure 7. The solubility of $Zn_3 (PO_4)_2$ compared to that of Zn minerals and soil Zn.

From Fuller, 1977 (94)

these factors are discussed, it should be emphasized that the soils themselves contain some zinc (10-300 mg/kg) that moves through the soils, finally entering underground water or lodging in the soil as insoluble or relatively slowly soluble compounds. Zinc in these compounds may be re-released by man's activities, specifically, by the disposal of acidic or acid forming wastes on soils. In some cases, particularly newly developed agricultural lands in arid regions which have not been previously leached, the natural migration in itself may be sufficient to pollute the groundwater beyond human use. In other instances climatic conditions, particularly rainfall, is one highly significant factor in natural soil contamination since it may provide the vehicle for movement or may have previously leached most of the readily soluble materials out of the soil.

It is very difficult to draw a definitive dividing line between those factors which increase or decrease the rate of mobility of the ions through soils. A factor which may increase the mobility of the ion in one soil may have no effect or an opposite effect in another soil. Some of the parameters which would influence the mobility of the zinc ions are: hydrogen ion activity, particle size distribution of soils, pore size distribution, presence of lime in soils, presence of hydrous oxides in soils, climate, and aerobic or anaerobic conditions of soils (94).

1. Hydrogen Ion Activity (pH)

The rate of mobilization of zinc ions may be expected to be influenced by the pH values of soils. In soils of acidic pH values, zinc salts ionize and thus can migrate easily. In neutral or alkaline soils formation of soluble salts such as zinc hydroxide would be favored, which would decrease the rate of migration of zinc (94).

The disposal of solid or liquid wastes on lands is also a major factor which should be considered while determining the movement of zinc or other metals in the soils. Prolonged discharge of highly acidic or highly alkaline wastes would alter the soil pH, thereby influencing the migration of the zinc.

2. Particle Size Distribution of Soils

The immobilization of metal ions in general involves both physical and chemical reactions on the surfaces of soils. The greater the surface area available, the greater is the potential for metal ions to adsorb on the surface. Hence, finer soil materials (silts, clays, and colloids) would have greater affinity to immobilize zinc as compared to the coarser materials such as sands and gravels (94).

3. Pore Size Distribution

Since water in soil pore spaces is the vehicle in which soluble constituents move, and because soil water moves more rapidly through larger than through smaller pore spaces, the pore size distribution of a soil has a profound influence on migration of metal ions (94).

4. Presence of Lime in Soils

As mentioned earlier the mobility of zinc ions would be greatly dependent upon the pH values of soils. The presence of natural or artificially added lime in soil would increase the pH value, and the rate of movement of zinc would therefore be decreased, due to the formation of insoluble zinc carbonate (94).

5. Presence of Hydrous Oxides in Soils

The presence of hydrous oxides of iron, aluminum, and manganese in soils contributes significantly towards the adsorption of zinc ions in soils by the continued formation of hydrous oxide-zinc combination compound.

$$2FeO.OH + Zn^{++} \longrightarrow ZnFe_2O_4 + 2H^+$$

Therefore, greater concentrations of hydrous oxides in soils would lead to increased retention of zinc (94).

6. Climate

Climatic conditions at a particular geographic location should be considered when determining the rate of migration of zinc in soils. High rainfall will increase migration. Torrid climates favor the formation of oxides and hydrous oxides in soils which are responsible for slowing the migration of metal ions (94).

7. Aerobic and Anaerobic Conditions

The mobility of zinc in soils would depend upon the availability of oxygen. In general, anaerobic soil conditions promote the mobility of zinc as compared to aerobic soil conditions (94).

XVI. SAMPLING AND ANALYSIS

Zinc has not been analyzed as frequently as other trace metals in biological systems and environmental matrices. However, there are a variety of methods available for carrying out its determination. These include spectrophotometry, titrimetry, emission spectrography, polarography, fluorometry, x-ray fluorescence spectrometry, atomic absorption spectroscopy, and neutron activation analysis. At present, atomic absorption spectroscopy (flame and flameless) seems to be extremely promising. It is a fast and sensitive method for the analysis of metals in microgram quantities and can be used for the determination of zinc in biological as well as environmental samples. Another highly sensitive and specific technique for the detection of trace heavy metals is neutron activation analysis which has recently been developed and applied towards the determination of zinc in various samples.

Despite the fact that many methods of determining zinc are available it should be emphasized, however, that these techniques measure the total zinc, and are not capable of distinguishing various zinc compounds from each other. Therefore, none of the methods described in this section can be regarded as specific to zinc chloride.

The methods of sampling and analysis described in this section are selected ones, which are more currently used for the estimation of zinc, and only papers appearing in the literature after 1960 have been included.

This chapter is divided into three sections viz., determination of zinc in A) air, B) biological samples, and C) environmental matrices (soil, vegetation, sewage, etc., excluding air). Since the sampling techniques vary considerably depending upon the analytical method employed, these are discussed separately under each method.

A. DETERMINATION OF ZINC IN AIR

The determination of zinc in air involves two steps: atmospheric sampling and analysis. These steps are described as follows:

1. Atmospheric Sampling

Common techniques for collecting particulate matter and for sampling fumes and dust containing zinc should be applicable for sampling of zinc chloride fumes in air. The method used for sampling zinc oxide in air may be applied for collecting zinc chloride fumes in air (98).

The sampling train consists of a membrane filter and a vacuum pump. The filter is a 0.8 μm pore size mixed cellulose ester membrane attached to the battery operated personal sampling pump worn by the worker, permitting sampling without interference to the worker.

The general methods for "respirable" dust sampling have been reviewed by Lippmann, 1970 (99).

2. Analysis

Several methods have been used for the determination of zinc in air, including atomic absorption spectrophotometry, polarography, and x-ray spectroscopy. Because of its speed and accuracy, atomic absorption is becoming one of the most important techniques for the determination of zinc.

a. Atomic absorption spectrophotometry

The sample, collected on a cellulose membrane filter, is ashed using concentrated nitric acid to destroy the organic matrix. Once the ashing is complete, as indicated by a white residue and following several minutes on a high temperature hot plate (400°C), the residue is converted to the chloride form by 3 successive evaporations with hydrochloric acid. The ash is then dissolved in dilute hydrochloric acid maintaining a pH of 1. The sample is then aspirated in an oxidizing air-acetylene flame of an atomic absorption spectrophotometer.

The optimum working range is 0.025-2 μg Zn/ml. The sensitivity is 0.025 μg Zn/ml (99,100).

b. X-ray spectrometry

The air sample is taken on almost any size or type of flat-surfaced filter paper whose sampling efficiency has been established. The entire sample or an aliquot is cut to convenient size, placed in a sample holder, backed by a 0.48-cm Lucite block, and introduced into the x-ray chamber. The goniometer is set at the peak of the most intense line for the element sought, the x-ray is activated, and three counts are obtained and averaged for each sample. Samples containing microgram quantities of zinc can be determined (101).

c. Polarographic method

Air samples are taken on Millipore filters or 20 x 30 cm glass filter sheets. The complete Millipore filter is digested with 50% nitric acid. The acid solution is dried and ashed at 450°C for 30 minutes. The residue thus obtained is dissolved in 0.1 N sodium hydroxide or 1.0 M potassium tartarate electrolyte. The half-wave potential is observed with a polarograph. Concentrations of zinc in microgram quantities can be determined (102).

B. DETERMINATION OF ZINC IN BIOLOGICAL SAMPLES

There are several methods available for the analysis of zinc in biological samples, some of which are presented here. Owing to the variation in sampling methods for different analytical procedures, the former are discussed under individual procedures.

1. Atomic Absorption Spectrophotometry

Atomic absorption spectrophotometry has been successfully employed for the determination of zinc in biological samples (blood, urine, hair) and foodstuffs (100,103,104).

a. Blood

Hemolysed whole blood is treated with a mixture of nitric acid, perchloric acid, and sulfuric acid. The acid solution is heated to 150°C, then to 200°C to fuming, and finally to 300°C to dryness. The residue is dissolved in hydrochloric acid and the acid solution is extracted with triisooctylamine in isobutyl methyl ketone. The organic layer is aspirated into an oxidizing air-acetylene flame of an atomic absorption spectrophotometer.

This method requires about 2 ml of blood sample. Concentrations in micrograms can be determined with a precision of better than 8 percent (103).

b. Urine

Urine samples are treated with glacial acetic acid (1 part glacial acetic acid to 100 parts urine) to prevent precipitation of the urine salts. The urine is then diluted with equal volumes of distilled water and aspirated directly into the atomizer of an atomic absorption spectrophotometer. The detection limit of this method is below 10 μg of zinc per liter (100).

c. Hair

The hair sample is thoroughly washed and dried to remove surface contaminants and is placed in a platinum dish. The dish is then placed directly on the heating element of an electric burner controlled to medium heat and left for approximately 5 minutes, after which it is placed in a muffle furnace at 500°C until the hair is completely ashed. After ashing, the sample is dissolved in 10% nitric acid and the acid solution is determined by atomic absorption in an air-acetylene oxidizing flame. Concentrations of zinc at mg/g of hair sample can be determined (100).

d. Food

The food is homogenized in a blender and is then digested with concentrated nitric acid until a solution is obtained. The solution is dried to a residue which is then ashed in a muffle furnace at 500°C overnight. The ashed sample is then dissolved in a mixture of nitric acid and hydrochloric acid. The acidic solution is aspirated into an oxidizing air-acetylene flame of an atomic absorption spectrophotometer (100).

2. Flameless Atomic Absorption Spectrophotometry

The flameless atomic absorption spectrophotometry has been used to determine small amounts of zinc and other metals in biological samples. It is one of the most recent techniques in atomic absorption spectroscopy. The method is simple, rapid and accurate and requires no sample pretreatment. It has been used successfully for the determination of zinc in blood and urine (104).

The blood sample is collected and allowed to clot for up to one hour at room temperature, centrifuges for 10 minutes and the serum is then transferred to screw cap vials and frozen until analyzed. The urine sample is collected in a polyethylene bottle and frozen until analyzed (105).

The burner of an atomic absorption spectrophotmeter is replaced with a carbon rod atomizer. A 1-µl sample is placed in the center of the carbon rod atomizer, and by selection of time and voltage settings, the sample is dried without boiling, then ashed, and finally atomized and swept into the light path by the flow of nitrogen. The optimum voltage and time settings for each of the three steps as reported are: (1) drying: 2.5 volts for 20 seconds; (2) ashing: 7.5 volts for 22 sedonds; and (3) atomizing: 7.0 volts for 2.5 seconds (104).

The detection limit is 10 µg of zinc per 100 ml sample (104).

3. Gamma-Ray Spectrometry

Gamma-ray spectrometery has been used to determine small amounts of zinc in biological tissues (human heart and liver) and in hair (105,106).

Tissue samples are charred with concentrated sulfuric acid. The mixture is heated until the solution is homogeneous, and 30% hydrogen peroxide is then added in small portions with heating between additions until fumes of sulfur trioxide are observed. The mixture is then cooled. This procedure destroys the organic matter and is completed when the solution does not change to a darker color on cooling. The solution is then treated with hydrobromic acid and distilled to remove antimony, arsenic, mercury, selenium, and tin as the volatile bromides. The remaining residue is treated with phosphoric acid, 3N hydrochloric acid and 0.3% hydrogen peroxide and passed through an ion-exchange column. The column is eluted with 0.1 N hydrochloric acid containing 0.3% hydrogen peroxide, and then with water containing 0.3% hydrogen peroxide. The eluate is then passed through a cation-exchange column and eluted with 6N hydrochloric acid containing 0.3% hydrogen peroxide. This eluate is used for the determination of zinc (105,106).

The γ-spectrometric determinations are made with a transistorized 512-channel pulse height analyzer, using zinc^{65} nuclide (half-life 245 days, γ-energy 0.51 millielectron volts) (105,106).

4. Neutron Activation Analysis

Traces of zinc can be determined in blood and other tissues by neutron activation analysis (107).

The weighed blood or other tissue samples (about 0.1 g) are inserted in polyethylene pill packs and these packs, together with others containing known amounts of zinc (of the same order as that present in the biological samples) are exposed to a high neutron flux in an atomic pile. The irradiated pill packs are dissolved in a mixture of sulfuric and nitric acids; and carrier zinc (about 50 µg) is added to the solution which is then buffered at pH 5.5. The zinc, including the Zn^{69m} produced by the irradiation, is then quantitatively extracted by diphenylthiocarbazone solution and freed as far as possible from radioactive contaminants. The amount of Zn^{69m} is then determined by a scintillation counter in conjunction with a pulse height analyzer (107).

C. DETERMINATION IN ENVIRONMENTAL MATRICES

Techniques used to determine zinc in biological samples are also applicable for environmental samples. Determination of zinc in air has been described earlier in this chapter. In this section the analysis of zinc in soil, vegetation, sewage, industrial effluents, and several standard reference materials (orchard leaves, bovine liver, coal, flay ash, and fuel oil) are discussed. Among the several available methods there are two major instrumental techniques which have been recently used for the analysis of zinc in these samples viz., atomic absorption spectrophotometry and neutron activation analysis. These methods are as follows:

1. Atomic Absroption Spectrophotometry

This method has been used for the determination of zinc in sewage sludges and in trade effluents (108,109).

a. Trade effluents

The samples of effluents are aspirated into an air-acetylene oxidizing flame of an atomic absorption spectrophotometer either directly without any pretreatment or after acidification with nitric acid (108).

b. Sewage sludges

The dried sludge samples are heated to redness in a silica crucible for one hour. After cooling, the samples are dissolved in 50% hydrochloric acid and aspirated into an air-acetylene flame of an atomic absorption spectrophotometer (109).

2. Neutron Activation Analysis

Neutron activation analysis is a highly sensitive method for the detection of trace heavy metal pollutants in environmental materials. The sampling techniques for various environmental matrices are described as follows:

a. Soil and vegetation

A known amount of the soil sample (air-dried at room temperature) or a vegetation sample (dried in oven at 65°C) is sealed in a clean polyethylene envelope and wrapped in aluminum foil. The sample is then placed in a quartz tube and irradiated for 60 hours, after which the irradiated sample is then dissolved in ice-cooled fuming nitric acid. Further dissolution is accomplished by adding concentrated hydrochloric acid followed by 30% hydrogen peroxide. The solution is subjected to radiochemical separation by ion exchange methods and then determined by γ-ray spectrometry.

The sensitivity of the method is 0.15 ng with the error involved in the results at the maximum $\pm$ 10% (105).

b. Standard reference materials

The following method has been used by the National Bureau of Standards. The samples to be analyzed are sealed in quartz vials and irradiated at a neutron flux of approximately 6 x 10^{13} neutrons per cm^2 per second. After irradiation, the sample activity is allowed to decay for a few hours to minimize the beta activity induced in the quartz vials. The vials are washed in dilute nitric acid, cooled to liquid nitrogen temperature and then opened at one end. The samples are weighed into a ceramic combustion boat, ignited with a gas torch in the presence of oxygen flow, and allowed to burn smoothly. After combustion, the combustion boat is enclosed in a tube furnace, and a stream of nitrogen is used to flush the system for 5 minutes at a flow rate of 20 ml/minute. A carbon monoxide stream of 15 ml/minute is adjusted to pass over the sample ash, and the furnace temperature is set at 1180°C for 40 minutes. Under these conditions, zinc is reduced to its elemental form and is collected in a liuqid nitrogen trap. The metal is dissolved in a mixture of concentrated nitric and hydrochloric acids. The solution is buffered with ammonium hydroxide and acetic acid and from this solution the sulfide is precipitated by reacting with ammonium sulfide solution. The sulfide is filtered and activity is then determined by counting the precipiate directly on a high resolution Ge(Li) detector, connected to a pulse height analyzer. Concentrations of zinc in micrograms per gram of sample have been determined by this method (110).

XVII. ENVIRONMENTAL IMPACT

Zinc chloride is produced as a smoke from HC smoke pots for screening purposes by the U.S. Armed Forces. The environmental effects of zinc chloride will depend upon the quantities dispersed in the use of the smoke generators, the frequency of smoke generating operations, and the environmental and meteorological conditions at a particular site. There are no data available indicating the rate of fallout and deposition of the zinc chloride, nor is there any information relating to the area which is affected by the dispersion of the smoke during an operation. Several factors which govern the dispersion, transport, and accumulation of zinc chloride in the environment include meteorological conditions, geology, hydrology, and surrounding environments of the field where the smoke is produced. In normal operations, assuming that two smoke pots (with an HC mixture charge capacity of 13.6 kg each) are used, each with a burning time of 12-20 minutes, about 1 kg of zinc chloride may be emitted. The smoke pots are usually placed about 70 meters apart from each other and at a distance of about 150 meters from the target. Under suitable meteorological conditions with a wind speed of 1-13 km/ph, the smoke rises to about 16 meters (11). Using these dimensions (150 x 70 x 16 meters), approximate average concentration of the zinc chloride smoke in the area would be 65 mg/m^3 (3-6 $mg\text{-}min/m^3$). It should be noted that these estimates are only speculative and not meant to represent the actual field concentrations. Cullumbine (7) has estimated that personnel may be exposed to atmospheric concentrations of 85 mg/m^3 at a distance of 180 meters from the source and to about 13 mg/m^3 at 900 meters under suitable meteorological conditions at night. In efficient flank screening by day, zinc chloride concentration at 90 meters is expected to be 47 mg/m^3 and at 900 meters approximately 0.9 mg/m^3.

Depending upon the location and surrounding environment of the site of smoke generating operations, zinc chloride would be expected to settle down to the ground, plants, vegetation, and waters, the ground being the main target. In the worst case, the ground around the generators may be contaminated with zinc chloride concentrations of 100 mg/m^2 of soil surface (assuming 1 kg of zinc chloride produced from 2 smoke generators falls on an area of 150 x 70 meters). The concentrations will rapidly be exceeded at a given site if the smoke generating operations are continued.

After deposition of zinc chloride on soils, its migration or mobilization would be governed by many factors. Before these factors are discussed it is imperative to point out that soils themselves contribute to various concentrations of zinc; background levels range between 10-300 mg/kg (94).

Zinc chloride in the presence of moisture will occur as zinc ion. The factors which influence the mobility of zinc ions in soils are: hydrogen ion activity, particle size distribution of soils, pore size distribution, presence of lime in soils, presence of hydrogen oxides in soils, climate, and degree of oxygenation of soils. These factors have been discussed in detail in Section XV on Occurrence, Dispersion, and Fate in the Environment. In general, the mobility of zinc in acidic soils is greater than in neutral or alkaline soils. Movement of zinc to 30 cm has been observed in an acid soil which had received a surface application of 16.8 metric tons/ha of sewage sludge(96). Practically all of zinc remained in the surface 20 cm of soil

following application of 84 metric tons/ha of sewage sludge for 12 years (111). There are also data showing evidence of movement of zinc below 15 cm in soil after application of 44-166 metric tons/ha of sludge over a 3-year period (97). Further leaching of zinc into streams of water supplies will depend on the quantity of rainfall and the level of the water table at the site.

Fallout of zinc chloride from the smoke on flowing rivers and streams would not pose any problem, but it would accumulate in still waters like ponds. For point of reference, assuming that all of the zinc chloride produced by two HC smoke pots at one time falls on a pond of 150 x 70 x 16 meters, the concentration in water of background zinc would be augmented by about 65 µg/1. These levels would be exceeded if the operations are continued for extended periods.

Since actual estimates of the quantities of zinc chloride released in the environment from smoke generating operations are not available, a general range of approximate concentrations will be employed here in an attempt to evaluate the impact of zinc chloride by comparison with known effective levels. Following is a synopsis of the known effects of zinc chloride which could be encountered by repeated generation of the smoke:

A. EFFECTS ON HUMANS

The lethal dose of zinc chloride smoke is not known but has been estimated as 50,000 mg/min/m^3. Such concentrations are not likely to be encountered under ordinary field exercise conditions. In a closed room of 3 m^3, however, this concentration can be achieved by one smoke pot in 2-3 minutes. At concentrations above 80 mg/m^3 for 2 minutes, volunteers had slight nausea and cough; at 120 mg/m^3 for2 minutes, irritation of nose, throat, and chest, with cough and nausea were noticed (7).

B. EFFECT ON DOMESTIC WATER SUPPLY

The U.S. Public Health Service Drinking Water Standards of 1962 set a limit of 5 mg/1 of zinc as acceptable in water supplies. World Health Organization and European standards are similar (67). The normal human intake of zinc is estimated at 10-15 mg per day. Communities using water supplies containing 11-27 mg/1 reported no untoward effects. Spring water in Missouri containing 50 mg/1 of zinc was used for a long time without reports of harmful effects. Very high concentrations of zinc in water can be toxic. A concentration of 675-2280 mg/1 zinc (as zinc sulfate) has been found to be emetic (67).

Concentrations as low as 5 mg/1 of zinc in water cause a greasy film on boiling (67). Therefore, from esthetic considerations the levels in domestic water supplies should be below 5 mg/1.

All readily soluble salts of zinc have an unpleasant, astringent taste and can be detected in less than dangerous amounts in drinking water. In tests performed by a taste panel, 5 percent of the observers were able to distinguish between water containing no zinc and water containing 4 mg/1 zinc as zinc sulfate; the taste threshold of 50 percent of the panel was 18 mg/1.

which had a bitter or astringent taste. The taste was less noticeable in spring water, the median threshold being 27 mg/1, but the most sensitive 5 percent of the panel were able to detect zinc at 6 mg/1 (67).

C. INDUSTRIAL WATER SUPPLIES

Water supplies containing zinc cannot be used in industries producing acidic drinks like lemonade because zinc citrate and other organozinc compounds may be formed which would be toxic.

D. EFFECTS ON PLANTS

While low concentrations of zinc are a nutritional requirement in most crops, high concentrations may be toxic. Concentrations of 3 mg/1 zinc in nutrient solutions have been found to be toxic to orange and mandarin seedlings; 5 mg/1 is toxic to flax and 10 mg/1 is toxic to water hyacinths. Zinc sulfate at levels of 25-100 mg/1 has been found to be toxic to oats (67). Concentrations of 6.5 mg/g zinc in soils considerably reduce the yield of grass (45).

During an observation period of 18 days, 54-436 mg/1 of zinc in nutrient solutions delayed germination and greatly retarded the growth of cress and mustard seeds in solution culture (67).

Zinc at 16-20 mg/1 produced iron deficiency in sugar beets and at a concentration of 2.5 mg/1 produced iron deficiency in oats. The Peking variety of soybeans was killed at 0.4 mg/1, whereas Manchu variety was killed at 1.6 mg/1 zinc (66).

From the estimates of the amount of zinc chloride released from one or two HC smoke pots, it appears that phytotoxic concentrations may not be produced in the environment from occasional use. However, toxic levels may be reached if frequent and continuous smoke generating operations are involved at the same site.

E. EFFECTS ON AQUATIC ORGANISMS

Zinc can enter waters directly as fallout from zinc chloride smoke or leaching from soils. Leaching may not be a problem if the soil is neutral or alkaline, since zinc is not readily mobile in these soils. When the soil is acidic zinc may leach into the water supplies. Fallout of zinc chloride on flowing waters such as rivers and streams should not be hazardous since toxic concentrations will not be accumulated in these sources. Some problems may be encountered in the case of still waters such as pond. From the use of two smoke pots at one time, assuming that all the zinc chloride produced will fallout on a 150 x 70 x 16 meters pond, the concentrations of zinc may attain 65 µg/1, excluding the amounts already present in the pond. Although this concentration is safe to aquatic organisms, continuous generation of the smoke at one site may increase the levels to toxic limits. It should be pointed out that these are only estimates, just for comparison purposes. The exact amount of zinc chloride contamination will depend upon the nature, frequency, and location of the operations.

Toxic concentrations of zinc compounds cause adverse changes in the morphology and physiology of fish. Acutely toxic concentrations induce cellular breakdown of the gills, and possibly the clogging of the gills with mucus. Chronically toxic concentrations of zinc compounds, in contrast, cause general enfeeblement and widespread histological changes to many organs, but not to gills. Growth and maturation are retarded (66).

Young carp are killed within 24 hours by 1.0 mg/l of zinc chloride in tap water. The highest concentration of zinc chloride tolerated by young eels for more than 50 hours is 0.14 mg/l, and 0.65 mg/l as zinc is lethal to eels in about 12 hours. The 96-hr LC_{50} value for bluegill sunfish exposed to zinc chloride is 8 mg/l of zinc at normal oxygen tensions, but when the dissolved oxygen is periodically lowered to 2 mg/l, the LC_{50} is only 4.9 mg/l as zinc. Exposure to 17 mg/l of zinc chloride for one hour has no detrimental effect on minnows. Concentrations of 0.25 mg/l of zinc chloride is lethal to hard clams during 48 hours while 0.17 mg/l produces 50% mortality during similar exposure. *Daphnia magna* are killed at concentrations of 1.5 mg/l of zinc chloride (61a).

F. EFFECTS ON DOMESTIC ANIMALS AND WILDLIFE

Zinc has been recognized as an important dietary element for humans as well as animals. The lack of trace amounts of zinc in the diet can produce various disease syndromes (44). Therefore, the physiological effects of zinc must be considered on the basis of whether the disease syndrome is produced by an excess or a lack of zinc in the diet.

Zinc chloride generated as a result of smoke producing operations can become available to domestic animals and wildlife through fallout on water and grazing areas. Grasses, forage plants, and other vegetation and plants can accumulate zinc either as a result of direct fallout or through absorption from the soils. Treatment of soils with 150 metric tons/ha of a sludge containing 570 mg/kg zinc resulted in 100 µg/g zinc in healthy perennial rye grass. A general toxic limit for zinc in plant dry matter is estimated at 500 µg/g (45).

Concentrations of 500 µg/g zinc in grass are unlikely to be toxic to livestock (45), and excess of these levels would be toxic to grass itself before it is consumed by the animals. Chronic ingestion of zinc in ground and surface waters had no adverse effects on domestic animals. Waters near the large zinc producing areas of Missouri, Oklahoma, and Kansas containing 0.9-50 mg/l zinc were consumed by horses, cattle, and hogs without any adverse effects (44).

The toxic levels of zinc chloride in the grazing areas and in drinking waters would be attained only if the same grounds are used repeatedly for smoke generating operations. The use of two smoke pots once in an area of 150 x 70 meters would contribute 100 mg zinc chloride/m^2 of soil surface. It should be noted that an application of about 9 g/m^2 results in 100 µg/g zinc in grass (45). Assuming that no background levels occur in the soil, in order to reach toxic levels (> 500 µg/g dry grass matter) for grass and for livestock it will require the use of two smoke generators for 450 times.

Since average soil background levels of 10-300 mg/kg are documented, toxic concentrations of zinc chloride would be reached in less than 450 usages of the 2 smoke pots.

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XVIII. TECHNICAL SUMMARY

Zinc chloride was first prepared by Glauber in 1648. It is a white, odorless compound composed of deliquescent granules or fused pieces or rods. Zinc chloride is very soluble in water, acetone, alcohol or glycerol and its solutions are fluorescent (1,2). It has been commonly used in the military as a smoke screen to conceal personnel but is also used in galvanizing, welding, textiles, wood preserving and in other industries (4,5,31) This Problem Definition Study focuses on the physical and chemical properties, toxicology, pharmacokinetics, environmental fate and impact, and occupational health and safety aspects of zinc chloride. Following is a summary of the reviewed literature on zinc chloride.

I. GENERATION OF SMOKE

Zinc chloride is generated with military smoke pots or munitions. Hexachloroethane (HC), zinc oxide, and grained aluminum or calcium silicide were allowed to react to produce the smoke which is mainly a fine cloud of particulate zinc chloride (6,7,8). Smoke pots containing 13.6 kg are usually placed about 70 meters apart at a distance 150 meters from the target to be screened and have a burning time of 12-20 minutes. The cloud produced rises to a height of about 16 meters (11).

II. HUMAN TOXICITY

The toxic effects of zinc chloride from inhalation, skin contact, eye and nose contact, and ingestion, and chronic ingestion of zinc are discussed.

A. Inhalation

Cases of acute zinc chloride intoxication resulting from inhalation of zinc chloride smoke have occurred in the military, in industry, and in civilian life (16). Smoke screens are produced by the reaction of hexachloroethane, zinc oxide, calcium silicide, and potassium nitrate. The resultant smoke is mainly a fine cloud of particulate zinc chloride as well as carbon monoxide, carbon dioxide, phosgene, hydrocarbons, and chlorinated hydrocarbons (6,7,18). Zinc chloride is hygroscopic, astringent, and highly corrosive to mucous membranes of the respiratory tract. It is especially dangerous in enclosed or confined spaces (6,7). Inhalation of zinc chloride in sufficient concentrations can cause cyanosis, pulmonary fibrosis, necrosis, and edema, subglottic stenosis, bronchopneumonia, and can prove fatal depending on the concentration and length of exposure (6,9,12-15,18-20). Smoke concentrations of 160 to 0.24 mg-min/m^3 caused minor nose, throat, and chest irritation. Moderate throat irritation, and some lung congestion was evident at dosages from 1700-2000 mg-min/m^3. At dosages of 20,000 mg-min/m^3 and greater severe respiratory tract irritation and pneumonia developed and usually required aggressive treatment. Exposure to 50,000 mg-min/m^3 and greater caused massive injury and was often fatal (8).

B. Cutaneous Toxicity

Skin contact with zinc chloride may cause burns and lesions of the forearms, fingers, and hands (22). Lesions generally develop at the site of a

recent, antecedent injury (21). A possible case of chronic zinc chloride intoxication has been reported. The symptoms included fatigability, anorexia, weight loss, and pain in the long bones (27).

C. Eye and Nose Toxicity

Accidental eye and nose contamination in 2 workers using zinc chloride soldering paste and galvanizing solution caused corneal edema, corneal scarring and opacities, cylinder refractive errors, and permanent loss of the sense of smell (23).

D. Oral Toxicity

A child who swallowed soldering paste containing 96% zinc chloride developed necrosis of the entire stomach from the esophogus to the pylorus. Corrosive gastritis and hepatic necrosis were revealed by autopsy (24). Persons have been reported to drink water containing 23 mg/l for prolonged periods without adverse effects. However, illness resulting from chronic ingestion of 5-8 mg/l has been reported (66).

III. TOXICITY TO EXPERIMENTAL ANIMALS

Acute and chronic effects of zinc chloride to experimental animals have been investigated.

A. Acute Toxicity

The effects of acute inhalation, percutaneous application, oral administration, and intraperitoneal injection of zinc chloride are presented.

1. Inhalation

Dogs exposed to high concentrations of zinc chloride smoke for 20 minutes developed hemoconcentration and pulmonary edema which were evident upon radiographic examination (33). The dosage (concentration x time) to kill 50% (LC_t50) of mice exposed to zinc chloride smoke was approximately 11,800 mg-min/m^3 but had to be reduced to 2,000 mg-min/m^3 before lung damage was no longer evident (7).

2. Percutaneous

Percutaneous application of 0.239 M zinc chloride onto the exposed skin of guinea pigs depressed growth but caused no mortalities (34).

3. Oral

The oral LD_{50} values of zinc chloride for mice, rats, and guinea pigs were 350, 350, and 200 mg/kg, respectively (34).

4. Intraperitoneal

Single intraperitoneal injections of 0.239 M aqueous zinc chloride into guinea pigs caused 6/10 deaths after 24 hours and 2 additional deaths by the seventh day after treatment (36).

B. Chronic Toxicity

The effects of chronic oral administration and intraperitoneal injection of zinc chloride are discussed.

1. Oral

Chronic ingestion of 0.25 or 0.5% zinc chloride in the diet by rats did not affect growth, mating, or the number of litters and offspring produced. The offspring also produced normal, healthy young. No pathological conditions were evident (38). Rats fed a synthetic diet, filtrate faction low in pantothenic acid and a daily dose of 4-6 mg zinc chloride by gavage for 20 weeks developed vitamin deficiency symptoms. This deficiency was characterized by: greying or rusting fur; crusting of the eye, nose, and tail; severe alopecia; and growth retardation (39).

2. Intraperitoneal

Rats given intraperitoneal injections of zinc chloride (10 doses of 1.2 mg each on alternate days) developed histological changes in renal tubular lining cells. The nuclei enlarged and there was formation of intranuclear inclusion bodies (40). Intraperitoneal injections of zinc chloride (10 doses of 0.6-1.2 mg each on alternate days) caused temporary paresis of the hindlegs and sphincters in rats. Morphological changes of the motor neurons of the spinal cord were observed (41).

IV. EFFECTS ON DOMESTIC ANIMALS AND WILDLIFE

Poultry and pigs exhibit a greater tolerance to dietary zinc than sheep and cattle. Diet composition can influence zinc toxicity in poultry. High zinc levels depressed growth and appetite, and induced arthritis and internal hemorrhages in weanling pigs. In sheep, 1000 and 1500 mg/kg of zinc caused reduced weight gains, decreased feed efficiency, and depressed feed consumption. High zinc levels induced tissue changes in sheep and cattle including subnormal liver copper levels, mild anemia, and changes in rumen metabolism. Ingestion of grass containing 500 µg/g zinc was not toxic to cattle but higher dietary zinc levels caused an abnormal appetite (44).

Birds have the tendency to concentrate ingested metals in their eggs and avian embryos are highly sensitive to trace metals (47). The percent survival of chicken eggs in injected with 1 ng/g to 10.0 mg/kg zinc chloride ranged from 83% to 9%; a concentration of 50 mg/kg caused 100% mortality. Chicks exhibited various changes. The percent of anomalous animals increased from 2% at a concentration of 0.1 mg/kg to 29% at 10.0 mg/kg. The median tolerance limit of zinc (as zinc chloride) was calculated to be 1.0 mg/kg (46).

Two way combinations of zinc with either mercury or cadmium exert purely additive effects on chick hatchability. The percent survival of chicks injected with a 1:1 mixture of zinc and cadmium was 78% at a concentration of 1 ng/g, and 24% at 1.0 mg/kg; 5.0 mg/kg caused 100% mortality. Eighty percent survived treatment with a 1:1 mixture of 1 ng/g zinc and mercury, and 8% with 10.0 mg/kg (47).

V. CARCINOGENICITY, MUTAGENICITY, AND TERATOGENICITY

The mutagenic, carcinogenic, and teratogenic effects of zinc chloride have been investigated in bacteria, fowl, and laboratory rodents.

A. Mutagenicity

Zinc chloride (0.05 M) did not inhibit growth of *Bacillus subtilis* and was not mutagenic (49). Tests on the ability of metal salts to affect DNA synthesis showed that 20-150 μM zinc chloride did not affect the accuracy of DNA synthesis but did decrease the rate of synthesis (48). RNA chain initiation was decreased by zinc chloride concentrations that inhibited overall RNA synthesis by 10-15%. Stimulation of RNA chain initiation was not evident at concentrations which inhibited RNA synthesis by 40-60%, concluding that zinc chloride was not mutagenic (50).

B. Carcinogenicity

The carcinogenic effects of oral, intratracheal subpleural, intraperitoneal, and intratesticular administration of zinc chloride in rodents and fowl have been investigated.

1. Oral

Pulmonary adenomas, and mammary, uterine, bone marrow and other cancers were observed in mice given potable water containing 10-20 mg/l zinc chloride for 5 or more months. The tumors were first evident after 6-8 months. Offspring of tumor-susceptible mice developed tumors more frequently than their parents. The frequency of tumors increased with each generation and the time of induction decreased (51).

2. Intratesticular Injection

The effects of intratesticular injection of zinc chloride in rodents and fowl are presented.

a. Rodents

Attempts to induce testicular teratomas in laboratory rodents by intratesticular injections of 1-5% zinc chloride and artificial cryptochism were unsuccessful. Hemorrhage, inflammation, necrosis, and the inhibition of spermatogenesis were evident (52-54). Implantation of zinc chloride into the seminal vesicles of mice resulted in inflammation, and necrosis but had no testicular effects (42). Hamsters injected with 5% zinc chloride died within 24 hours (52). Total testicular destruction was noted in Syrian hamsters injected with 4% zinc chloride. Embryomal carcinomas were isolated in 2/49 animals 10 weeks after treatment and were characterized by giant cells, large and convoluted nuclei, prominent nucleoli, and the absence of spermatogenesis in the seminiferous tubules (53).

b. Fowl

Intratesticular injections of 3-5% zinc chloride induced teratomas in a small percentage of fowl but only during a period of seasonal or photoperiodically induced gonadal growth (55,58). Inflammation, edema, hemorrhage, and necrosis were evident at the site of injection (55,58). A range of struc-

tures were identified in these teratomas which were similar to those found in human teratomas (56). Intratesticular injections of zinc chloride and chorionic gonadotrophic hormone over a prolonged period of time produced teratomas in only a small percentage of the birds treated (55).

C. Teratogenicity

Injection of zinc chloride solutions into the yolk sacs of chicken eggs induced serious changes in chicks and reduced survival and hatchability. This experiment is described in the section on Domestic Animals and Wildlife (46,47).

VI. EFFECTS ON AQUATIC ORGANISMS

The toxic effects of zinc chloride to freshwater and marine organisms has been investigated.

A. Freshwater Toxicity

Metal salts are found in most industrial wastes and are harmful in high concentrations. The toxicity threshold, the toxicant concentration that begins to cause mortality of zinc chloride to *Daphnia magna* was determined to be 1.1×10^{-6} molar (61). The toxicity threshold of *Lebistes reticulatus* under given environmental conditions was determined to be 0.33 mg/1 (62). The 48 hour lethal concentration (LC_{100}) and median lethal level (LC_{50} of zinc chloride to *Tilapia mossambica* was 20-22 mg/1 and 10-15 mg/1, respectively, when dissolved oxygen was 5.6-8.2 mg/1. The toxicity was reduced by 75% by the addition of 200 mg/1 calcium chloride. Mortality was decreased to 40% by increasing the oxygen content of the water to 12.3 mg/1 (63). The threshold values of toxicants depended upon environmental conditions such as dissolved oxygen. Periodic reduction of oxygen reduced the 96-hour LC_{50} of *Lepomis macrochinus* Raf. from 8.02 mg/1 to 4.9 mg/1 zinc chloride, and decreased the range between the highest concentration allowing survival and the lowest concentration causing death (64).

B. Marine Toxicity

Zinc chloride had a toxic effect on the survival and development of *Mercenaria mercenaria* embryos. The concentrations of zinc (as zinc chloride) that produced 0 (LC_0), 50 (LC_{50}), and 100% (LC_{100}) mortality were determined to be 0.095, 0.166 (0.138-0.175),* and 0.25 mg/1, respectively (68). When newly fertilized eggs or 6-hour blastulas of *Dendraster excentricus* were exposed to between 6.25×10^{-6} M and 1.0×10^{-2} M zinc chloride continuously or for 6, 18, or 24 hours, high concentrations inhibited cleavage while low concentrations significantly changed the developmental pattern (69). Similar results were obtained when *Arbacia punctulata* were exposed to different concentrations of zinc chloride in seawater for 17 hours or were transferred from a 100 mg/1 dilution to fresh seawater every 5 minutes (90). Treatment of *Paracentrotus lividus* eggs with various concentrations of zinc chloride for different periods of time stopped blastulation or caused immediate lysis. Surviving embryos exhibited a series of anomalies including over-developed ciliature, thickened ectoderm, and absence of the endoderm and secondary mesenchyme (71).

*Range was specified for LC_{50} only

VII. EFFECTS ON MICROORGANISMS

Zinc chloride has been shown to reduce survival and have a lethal effect on bacteria. *Bacillus megaterium* were exposed to 6×10^{-6} M zinc chloride or to 2000, 6000, or 24,000 rads of gamma radiation. The percentage survival decreased with increasing exposure time for both treatment modes. Combination of zinc chloride treatment and gamma irradiation had a synergistic effect, causing even greater reductions in survival by affecting cell growth and multiplication (72).

VIII. EFFECTS ON PLANTS

Immersion of leaves of *Zea mays* L. and *Lycopersicon esculentum* in zinc chloride solutions caused leaf and plant injury. *Zea* was more susceptible, the entire plant being involved by day 7. Injury was evident on 75% of *Lycopersicon* plants within 7 days (73).

Explants of cauliflower, carrots, lettuce and potatoes were exposed to 0.0, 0.5, 5.0, or 50.0 mg/l zinc chloride for 20 days. The growth of lettuce and carrot cultures was inhibited at 50.0 mg/l. Cauliflower was very sensitive and could not tolerate more than 0.5 mg/l. The treatment had no effect on potato explants (74).

Zinc in low concentrations is necessary for the normal growth of plants. However, excess zinc may be toxic to plants. Delayed germination and severely retarded growth was observed in cress and mustard seeds grown in a nutrient solution containing 54-436 mg/l. Concentrations of 3, 5, and 10 mg/l were toxic to orange and mandarin seedlings, flax, and water hyacinths, respectively (66). A general toxic limit for zinc in plant dry matter is estimated at 400-500 µg/g.

IX. PHARMACOKINETICS

The uptake, retention, distribution and excretion of zinc chloride in humans, experimental animals, and livestock have been studied after acute oral and intravenous administration of radioactive ^{65}zinc chloride (76-89). The pharmacokinetics of ^{65}zinc chloride in aquatic organisms has also been examined (90,91).

A. Humans

No reports on either pulmonary absorption of zinc chloride after inhalation of its smoke or percutaneous absorption of the compound are available. Oral administration of ^{65}zinc chloride to patients with various malignancies revealed that ^{65}zinc enters the blood stream rapidly (80). One half hour after intravenous injection, 90% of the administered dose had left the vascular space, and at one hour 4% of the dose remained in whole blood (22,79). By 24 hours, ^{65}zinc in whole blood was 4 times than in plasma. Whole blood ^{65}zinc levels were twice as high as plasma levels as much as 75 days after dosing (79). Uptake and distribution of ^{65}zinc was highest in th liver followed by the kidney, pancreas, and spleen (22,77). ^{65}Zinc turnover was highest in the pancreas followed by the liver and spleen. The biological half-life of ^{65}zinc in the liver was estimated to be 75 days (77).

^{65}Zinc was primarily eliminated through the intestine in the feces. Thirty days after intravenous injection, 18% of the administered dose was excreted in the feces but less than 1% was eliminated in the urine. Fifteen days after oral administration, 19 to 76% of the dose was excreted in the feces while 0.7 to 2.1% was excreted in the urine (22).

B. Experimental Animals

Zinc chloride is poorly absorbed through the skin as shown by application of ^{65}zinc chloride on the skin of guinea pigs. Less than 1% ^{65}zinc was absorbed in 5 hours (81). One study reported that 5% of the administered dose was absorbed by rats 24 hours after feeding (82). Recent work reported that 25% of the intubated dose was absorbed by the intestinal wall after 30 minutes and that this level of absorption was maintained for 7.5 hours. Absorption was greatest from the duodenum (27%) followed by the midjejunum (11%) and ileum (8%) (83). ^{65}Zinc was no longer detectable in the plasma of dogs 10 hours following intravenous injection.

In rats, the highest concentrations of ^{65}zinc were found in the kidney, liver and pancreas 4 days after intravenous injection of a single tracer dose of ^{65}zinc chloride (82). Similar results were found in rabbits given intravenous injections of ^{69m}zinc chloride. The greatest accumulations of ^{69m}zinc were found in the pancreas, liver and intestines between 2 and 20 hours after dosing (84). In mice, the ^{65}zinc concentration was highest in the liver between 45 minutes and 170 hours after injection (78). Similar results were found in dogs between 3 and 170 hours after dosing (78).

Mice excreted over 50% of the administered dose of ^{65}zinc in the feces in 170 hours. Only 2% was eliminated in the urine. About 25% of the injected dose of radiozinc was detected in the feces of dogs 12-14 days after treatment while only 1.2 to 4.7% of the ^{65}zinc was excreted in the urine in 15 days (85).

C. Livestock

Pigs were given intravenous injections of ^{65}zinc chloride. Over 90% of the ^{65}zinc in the blood was absorbed by the tissues within 1 hour (86).

The uptake of ^{65}zinc by the rumen tissue of lambs peaked 12 hours after intravenous injection of ^{65}zinc chloride and stable zinc chloride. Lambs which were maintained on a low zinc diet prior to oral administration of ^{65}zinc chloride and stable zinc, showed the highest concentration of ^{65}zinc per kg rumen tissue 48 hours after dosing. In a similar study, it was found that the concentration of ^{65}zinc per kg of rumen tissue was significantly higher than in abomasal, duodenal, and intestinal tissue levels (87).

Seven days after oral dosing, the net ^{65}zinc absorption by bull calves was 62% of the treatment dose. ^{65}Zinc concentrations were highest in the liver followed by the spleen, kidney, heart, small intestine, duodenum and lung. Increasing the zinc content of the diet of uncastrated calves from 38 to 238 mg/kg significantly ($p < .01$) decreased the ^{65}zinc content of the heart, testicle, rumen wall, and fundic abomasum. An increase from 238 to 638 mg/kg significantly increased ($p < .01$) the ^{65}zinc content of the pancreas, liver, kidney, tibial shaft and joint, duodenum, and small intestine (89).

In livestock, zinc is primarily excreted in the feces. Pigs excreted 75-90% of administered ^{65}zinc in their feces; 95% was excreted with a half-time of 100 days. Pancreatic, biliary, and duodenal excretion of zinc totalled 0.475% (86).

^{65}Zinc excretion by calves peaked 2 days after vial dosing. Calves fed diets containing 238 and 638 mg/kg supplemental zinc excreted 30% more ($p < .01$) ^{65}zinc in their feces than calves fed 38 mg/kg dietary zinc. The average daily fecal ^{65}zinc excretion rate 14 days after dosing was 32% of the peak daily rate (88,89).

X. UPTAKE AND DISTRIBUTION IN AQUATIC ORGANISMS

^{65}Zinc largely accumulated in the digestive tract, gills, and viscera of marine goby and filefish. In the short-necked clam, ^{65}zinc concentrations was highest in the gills and mantle; and continued to accumulate in these tissues and adductor muscle even after 30 days. In the mussel, ^{65}zinc content was highest in the adductor muscle, shell, and visceral mass and reached a constant level within 20 days. ^{65}Zinc concentrations in the sea urchin were highest in the digestive tract and were also highest when compared to the organs and tissues of the fish and mollusk species (90).

XI. BIOACCUMULATION

Zinc can accumulate in plants, wildlife and domestic animals, and aquatic organisms which are utilized by man. Application of zinc-containing sludge and fertilizer resulted in zinc accumulation in rye grass (45), corn (91), and grain, leaves, and legumes (92). Radioactive ^{65}zinc has been shown to accumulate in plants, depending on species, plant part, nutrient media, temperature, light, and soil conditions (66).

In a test pond, less than 1% of the applied ^{65}zinc was accumulated in seafood organisms, including clams, oysters, and scallops. Most was lost with water in an adjacent estuary and through pond sediments (93). ^{65}Zinc is accumulated in algae, plankton, and bacteria.

Domestic animals and wildlife on ^{65}zinc-contaminated grazing lands accumulate zinc in their beef, bones, flesh, and milk (66). Zinc in milk, meat, shellfish, and plants can become concentrated in man. The human body retains 0.67-1.3 mg zinc per year over a 45 year period (92).

XII. OCCURRENCE, DISPERSION, AND FATE IN THE ENVIRONMENT

Zinc is found as a mineral in the earth's crust, usually associated with other base metals. It also occurs in igneous rock. Dissolved zinc is found in waterways such as in zinc-mining areas and in seawater (66). Zinc occurs in such natural sources as man, wild animals, sea foods, meats, legumes, roots, leaves, fruits, grains, cereals, nuts and spices (92).

Smoke generating operations would be potential sources for dispersion of zinc chloride in air, soil, vegetation, and waters. Other potential sources are industrial effluents and wastes, and industries utilizing zinc chloride. In the environment, zinc chloride would undergo hydrolysis reactions forming various ionic species and other products. Zinc ion, chloride ion and other species are are formed by dissociation in water. Zinc ion forms several insoluble precipitates with carbonate, phosphate, and silicate ions (1,16,17,19,60,68,94).

All soils contain zinc. Movement of zinc ion in soil depends on pH, soil type, the zinc species formed, particle size distribution of soil, pore size distribution, presence of lime in soils, presence of hydrous ions in soils, climate, and aeration conditions of soil (1,4,5,31,94).

XIX. HAZARD ANALYSIS AND RECOMMENDATIONS

A hazard analysis of zinc chloride exposure and recommendations for additional research on the toxicological and environmental aspects of zinc chloride smoke exposure are reviewed in this section.

A. HAZARD ANALYSIS

Zinc chloride may be toxic if inhaled in high concentrations (see Table 3, page 22), ingested, or if it comes in contact with the skin, eyes, or nose. Exposure to 40 mg-min/m^3 of zinc chloride smoke has been reported to cause slight nausea and coughing. As evidenced by its uses, inhalation and skin contact would occur more commonly than oral intake. Almost all reports of zinc chloride intoxication have been the result of accidental exposure. When zinc chloride smoke screens are generated, the potential hazards arise from skin contact and inhalation by exposed persons. In addition, the risk of eye and nasal contamination is also very high unless proper precautionary measures are taken.

In reviewing the literature it was reported that the risks associated with zinc chloride smoke exposure can be reduced if used at moderate concentrations and if handled properly. The highest safe dosage has been taken to be 2,000 mg-min/m^3 which could be for a single exposure or repeated exposures to low concentrations during a 10 day period (7).

It has been suggested that under a given set of meteorological and geological conditions, and assuming no protective measures are taken, persons working at specified distances for a limited time could be exposed to zinc chloride smoke without adverse effects (7). During the night, the concentration of zinc chloride at a distance of 183 meters from the smoke pot is approximately 85 mg/m^3; at 914 meters that concentration is approximately 13 mg/m^3. Therefore, a person can remain at those distances for a maximum of 24 minutes and 2.5 hours, respectively. By day, the zinc chloride concentration at 91 meters is approximately 47 mg/m^3 and would permit 43 minutes of exposure time. At 914 meters, the concentration is approximately 0.9 mg/m^3 and a person could stay for 37 hours (7).

B. RECOMMENDATIONS

Although zinc chloride smokes and other zinc chloride-containing compounds have been used for many years, much of the data collected on the toxic effects of this substance have been derived from direct observation of the accidental intoxication of humans following exposure. Animal experimentation has been extremely limited. In several areas, information is scarce and further investigation derived from animal models, where possible, could be gathered.

1. Zinc chloride is hydrolyzed into zinc oxychloride and hydrochloric acid in the atmosphere and in the respiratory tract. It has not been determined if the toxic effects observed are due to the action of zinc chloride, zinc oxychloride, or hydrochloric acid individually or in combination. This should be determined. Moreover, zinc chloride smoke is usually produced from hexachloroethane, zinc oxide, and aluminum, or hexachloroethane, zinc oxide, and calcium silicide. Depending upon the method employed the smoke thus produced also contains other products such as aluminum oxide carbon particles, phosgene

and chlorinated hydrocarbons. The toxic effects of these products in zinc chloride smoke, at concentrations to which the personnel are likely to be exposed, should be undertaken. Although these constituents are not present in large quantities, they may either enhance or, in combination, contribute significantly towards the toxicity of zinc chloride smoke.

2. Although the effects of aqueous zinc chloride on skin and eyes are well established, knowledge of the effects of zinc chloride smoke upon contact with skin and eyes may be desirable.

3. The concentrations of zinc chloride around the smoke pots or and in the area covered by the screen, as well as the dimensions of the smoke screen produced have only been estimated. Determination of these concentrations and dimensions would enable a better perspective of the potential hazards to personnel exposed to zinc chloride smoke. In addition, the amounts of zinc dispersed into the environment, up to now only estimated, can be more accurately determined. Information on the number of times that a smoke screen may be used in a particular given area has not been available. With this information, a better understanding of the potential environmental impact of zinc chloride smokes would be possible.

4. To date, carcinogenicity studies have focused on the effects of intratesticular injections of zinc chloride in fowl and rodents. Chronic toxicity studies with experimental animals have primarily been concerned with chronic ingestion. The carcinogenic, mutagenic, histopathological, and other toxic effects of chronic inhalation of zinc chloride smoke need to be thoroughly evaluated. Bioassays using currently accepted protocols are recommended. Many of the human exposures to zinc chloride smoke occurred during World War II. Retrospective studies of exposed victims should now be instituted.

Specific toxicological studies that have not been performed on zinc chloride and the areas requiring further research are summarized in Table 21.

TABLE 21

Gaps in Toxicological Data on
Zinc Chloride Smoke

Acute LC_{50} inhalation	X
Eye and skin irritation	X
Subacute inhalation studies	X
Chronic inhalation studies	X

X - marks indicate that an adequate study has not been undertaken.

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4 - ISI SCISEARCH (searched on Oct. 5, 1977)

5 - Cancerline (searched on October 4, 1977)

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7 - Defense Documentation Center (received on September 25, 1977)

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Organizations Contacted

1. National Institute for Occupational Safety and Health
   Division of Criteria Documentation and Standards Development
   Rockville, Maryland 20852

2. General Electric Company
   Schenectady, New York

3. Mallinckrodt, Inc.
   Mallinckrodt and Second Streets
   St. Louis, Missouri 63147

4. National Institute of Enivronmental Health Sciences
   P. O. Box 12233
   Research Triangle Park
   North Carolina 27709

5. U.S. Army Ordnance & Chemical Center & School
   Chemical Directorate
   Aberdeen Proving Ground, Maryland 21005

Persons Contacted

1. Mr. Vernon E. Rose
   National Institute for Occupational Safety and Health
   Division of Criteria Documentation and Standards Development
   Rockville, Maryland 20852
   (301)-443-3680

2. Dr. J. J. Ferry
   Area Manager
   Industrial and Environmental Hygiene
   General Electric Company
   Schenectady, New York
   (518)-385-2604

3. Mr. Roger Hopkins
   Mallinckrodt, Inc.
   Mallinckrodt and Second Streets
   St. Louis, Missouri 63147
   (314)-895-5441

4. Dr. Warren T. Piver
   National Institute of Environmental Health Sciences
   P. O. Box 12233
   Research Triangle Park
   North Carolina 27709
   (919)-541-3471

5. Lt. Col. (Retired) James B. Mason
   U. S. Army Ordnance & Chemical Center & School
   Chemical Directorate
   ATTN: ATSL-CLC
   Aberdeen Proving Ground, Maryland 21005
   (301)-671-2844 or (301)-671-3556

6. Mr. William Russel
   Commanding Officer
   ATTN: STEAP-PE-E
   Aberdeen Proving Ground, Maryland 21005
   (301)-278-5622

7. Mr. Richard Taft
   National Institute for Occupational Safety and Health
   DTS, COSHI, IRS, C-19
   4676 Columbia Parkway
   Cincinnati, Ohio 45226
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