Acute:	NA
Chronic:	NA
Marine	
Acute:	NA
Chronic:	NA

References

Sax and Lewis 1987, Verschueren 1983, The Merck Index 1983, SPHEM 1986, EPA 1988

NA - Not Available

C. Fate and Transport

Complex formation, sorption processes, and bioaccumulation will determine the fate of copper in aquatic systems. Other variables such as pH, Eh, concentrations of organic materials, and availability of precipitating iron and manganese oxides will influence precipitation, dissolution, and most important, sorption processes.

Copper is usually concentrated in sediments of non-polluted (aerobic) water, where it is sorbed by clays, organic material, and iron and manganese oxides. Copper transported in the water column is usually associated with dissolved or suspended solids. The solubility of copper decreases substantially in anaerobic water. Most atmospheric copper is deposited in soils and surface waters through dry fallout and precipitation. Most copper in soils remains in the top few centimeters, sorbed to organic matter, clays, and iron and manganese oxides. The potential for migration of copper to ground waters is small, but may be of concern in highly porous areas or low pH (below pH 5) environments which have a high water table. Literature indicates that photolysis, volatilization, and degradation are considered insignificant in determining the fate of copper.

D. Ecotoxicology

Copper is ranked second to mercury in the magnitude of its ecotoxic effects on aquatic organisms. The principal toxic copper species is cupric ion (Cu^{+2}), although two hydroxy complexes ($CuOH^{+1}$ and $Cu_2OH_2^{+2}$) have also proven to be toxic (Howarth and Sprague 1977). The toxicity of copper in water is controlled primarily by alkalinity (which includes hardness), dissolved oxygen, chelating agents, humic

acids, pH, and suspended solids. In studies using several fish species, the maximum tissue copper concentrations were detected in the liver, followed by the gill, kidney, and muscle. In chronic studies encompassing a complete life cycle, brook trout (Salvelins fontinals), fathead minnows (Bromelas pimephales), and bluegills (Lepomis macrochirus) were most sensitive to copper in their early life stages (larval and juvenile). In addition to its effects on survival, copper also produces deleterious results in growth and reproduction. Inhibition of spawning and marked decreases in egg hatchability were observed in fish exposed to copper concentrations of 162 ug/l and 32 ug/l, respectively. According to freshwater data the lowest copper concentration at which acute or chronic effects may occur is 10 ug/l. LC_{50} values for freshwater invertebrates range from 5 ug/l (Daphnia hyalina) to 9,300 ug/L for the snail (Amnicola lycorias). Additionally, copper sulphate, which inhibits photosynthesis and plant growth, has been an important biocide used to control algae blooms in nutrient sensitive waters. In aquatic ecosystems copper contamination generally occurs in a melange with other heavy metals. The association of these trace metals with other xenobiotics poses the additional complexities of synergistic, antagonistic, and additive toxic responses.

The paucity of data exists regarding the effects of copper contamination in the marine environment. Shellfish are known accumulators of trace metals; studies using the clam (Venerupis decussata) showed the onset of adverse effects at 10 ug/l. In vertebrate tests embryos of the summer flounder demonstrated an LC_{50} at 38 ug/L. Since the complexing capacity of the marine environment is lower than the fresh water environment adverse responses to copper by marine organisms would be expected at levels similar to or below those demonstrated by freshwater species.

E. Human Toxicology

Ingestion of high levels of copper results in digestive disturbances (10 mg) and gastrointestinal ulcerations, hemolysis and hepatic and renal damages (<1 gram) (NRC 1977). Chronic exposure to excessive doses of copper generally results in accumulation of copper in the liver followed by hepatocellular damage both in animals and humans. The U.S. EPA has calculated an Acceptable Daily Intake (ADI) for copper of 3.7×10^{-2} mg/kg/day based on a human oral LOAEL of 7.6×10^{-2} mg/kg/day with an applied uncertainty factor of 2 (USEPA 1984, 1986). The U.S. EPA has also calculated an ADI for inhalation exposure of 1.0×10^{-2} mg/kg/day based on a TLV of 1.0 mg/m^3 for

copper dusts and mists with an applied uncertainty factor of 10 (ACGIH 1983 as reported in U.S. EPA 1984, 1986). The U.S. EPA has determined that there is insufficient data to assess the carcinogenicity of copper to humans (USEPA 1987).

- **Acute and Chronic Toxicology**

Copper has been found to accumulate in the liver lysosomes of mice and rats, resulting in hepatic damage. Rats maintain normal hepatic copper levels until a diet extremely high in copper is reached (Burka et al. 1966; Goldfesher 1967; Cal and Soucke 1971, as reported in NRC 1977). Dietary levels of 240-500 ppm are required to produce toxicosis in swine and rats (Boyden et al. 1938; Suttle and Mills 1966a; Wallace et al 1960, as cited in NRC 1977).

Haywood (1980) reported that rats treated with 2000 ppm copper (as copper sulfate) in the diet for 15 weeks developed hepatic and renal necrosis. The damaged tissue regenerated and the rats appeared to have developed tolerance to the metal (Haywood 1980).

There are limited data concerning the chronic effects of copper in animals. In a chronic feeding study (Howell 1959 as reported in USEPA 1987), rats accumulated copper in the kidney and liver when the diet was supplemented with 5000 ppm copper acetate. In a similar study, rats exposed to 1250 ppm cupric acetate in the drinking water for up to 902 days developed copper deposition in the liver, kidney, brain and intestines (Owen 1974).

The toxic intake level of inorganic copper for an adult male is over 15 mg/day (Burch et al. as reported in USEPA 1980). Copper toxicity produces a metallic taste in the mouth, nausea, vomiting, epigastric pain, diarrhea, laryngitis, bronchitis, anemia, and depending on the severity, jaundice, hemolysis, hepatic necrosis, azotemia, hematuria, oliguria, anuria, hypotension, coma, and death (Chuttani et al. 1965, Davenport 1953, as reported in NRC 1977). Vomiting and diarrhea induced by ingesting milligram quantities of copper generally protect the patient from the serious systemic toxic effects.

Ingestion of ten milligrams of cupric ions in a 60-90 ml drink produced abdominal cramps, vomiting, and diarrhea within 10-90 minutes of ingestion (Morbid. Mortal. Week. Reports. 1975, as cited in NRC 1980). Ingestion of more than gram quantities of salt such as copper sulfate results in gastrointestinal mucosal ulcerations, hemolysis, hepatic necrosis, and renal damage from deposition of hemoglobin and/or copper (Chuttani et al. 1967, Wahat et al. 1965, as reported in NRC 1977). Hemolysis has also been reported after applying solutions of copper salts to large areas of burned skin, or after

introducing copper into the circulation during hemodialysis (Holtzman et al. 1966, Lyle et al. 1976, as reported in NRC 1977).

Chronic exposure to excessive doses of copper generally results in accumulation of copper in the liver followed by hepatocellular damage. Toxic levels vary widely among species. Sheep are quite susceptible to high levels of copper in the diet; copper levels of 35 ug/g of feed have resulted in toxicity when fed over a period of nine months to one year (Fontenut et al. 1972, as reported in ASEPA 1980). Cattle given 2 g of copper sulfate in the diet daily did not experience toxic reactions (Cunningham 1931, as reported in USEPA 1980). Sheep accumulate copper in the liver in proportion to the dietary intake, while rats maintain normal hepatic copper levels until a diet extremely high in copper (1000 ppm) is reached (Milne and Weswig 1968, as reported in NRC 1977). Sheep consuming small but excessive amounts of copper manifest toxic effects when a threshold level of 3-15 times the normal liver copper concentration (or about 140 ppm) is reached. Effects include cytoplasmic vacuolation and necrosis of hepatocytes and increases in liver-related serum enzyme activities (NRC 1977). Hepatic damage frequently results in a sudden release of copper from the liver, causing a severe hemolytic crisis. Death may result from blockage of the kidneys by hemoglobin and subsequent kidney failure.

Dietary levels in excess of 250 ppm copper are required to produce toxicosis in pigs and rats (Boyden et al. 1938. Suttle and Mills 1966a, Suttle and Mills 1966b, Wallace et al. 1960, a reported in NRC 1977). Studies in mice and rats have revealed that copper accumulates in the liver lysosomes, perhaps causing a release of acid hydrolases and resulting in hepatocellular damage (Barka et al. 1964, Goldfischer 1967, Cal and Sourkes 1971, as cited in NRC 1977). Copper toxicosis in non-ruminants may not cause a hemolytic crisis, though pigs fed dietary copper levels ranging up to 750 ug/g suffered hypochromic microcytic anemia, jaundice, and marked increases in the liver and serum copper levels as well as serum aspartate amino transferase (Suttle and Mills 1966a, 1966b, as reported in NRC 1977).

A male infant receiving high levels of copper in the drinking water (350 ug/L - 790 ug/L) for three months developed behavioral change, diarrhea, progressive marasmus, and symptoms of "pink" disease (prostration, misery, red extremities, hypotonia, photophobia, and peripheral edema). Symptoms subsided following three months treatment (Salmon and Wright 1971, as reported in USEPA 1977). In general, the metallic taste and formation of insoluble copper compounds in water with high copper content prevent ingestion of high levels of copper.

Typical metal fume fever, characterized by chills, fever, aching muscles, dryness in the mouth and throat, and headache, has been

reported in several workers handling copper oxide powder in a paint factory. Copper acetate dusts have caused complaints of sneezing, coughing, digestive disorders, and fever. Dust concentrations were not provided. Studies of Chilean copper miners have not revealed unusually high serum copper concentrations despite chronic exposure to copper sulfide and oxide dusts (Fishburn ans Zenz 1969, Gleason 1968, Schiotz 1949, as reported in NRC 1977).

Contact dermatitis associated with copper has been reported, but observations of scores of smelter and refinery workers have not revealed any significant incidence of dermatitis that could be traced to exposure to either copper or many of its inorganic compounds (Saltzer and Wilson1968, Pinto 1947, as reported in NRC 1977).

There is very little evidence in the literature to suggest that copper has a teratogenic effect in either animals or humans.

Studies have not found that copper itself has a mutagenic effect in either animals or humans; however, one report suggests that copper may increase the mutagenic activity of several enediol reductions such as ascorbic acid in the TA100 strain of Salmonella typhimurium (USEPA 1980).

There is little evidence in the literature to suggest that copper has a carcinogenic effect in either animals or humans. One case report indicated that vineyard workers in France, Portugal, and southern Italy developed granulomas in the liver and malignant tumors in the lung following exposure to copper sulfate sprays mixed with lime (Pimental and Morgues 1969, as reported in USEPA 1980). The route of exposure prevented accurate exposure estimates.

F. Pharmacokinetics

Copper may be absorbed dermally, through the gastrointestinal tract, or through the lungs, through inhalation of copper compounds is of minor significance compared to other routes. Most absorption of copper in humans takes place in the stomach and the duodenum. Copper absorption appears to be regulated by the intestinal mucosa, and maximum copper levels occur in the blood serum within one to three hours of oral intake (USEPA).

Approximately one half of the copper in the diet is excreted directly in the feces (Steinleib 1967, Strickland et al. 1972, as reported in NRC 1977). Animal studies have revealed two mechanisms of copper absorption, an energy-dependent mechanism and an enzymatic mechanism (Crampton et al., as reported in USEPA 1980). Many

factors affect copper absorption including competition for binding sites with zinc, interactions with molybdenum and with sulphates, chelation with phytates, and inhibition by ascorbic acid (USEPA 1980). Absorbed copper is rapidly transported to blood serum and taken up by the liver, where it is bound to liver metallothionein. Copper is later released and incorporated into the copper protein ceruloplasmin. Any remaining free serum copper binds to albumin or amino acids, is used to maintain erythrocyte copper levels, or is sequestered by lysosomes (Evans et al. 1973, Evans 1973, Starcher 1969; Bearn and Kunkel 1954, 1955, as reported in USEPA 1980). Between 32-70% of the copper ingested is absorbed through the gastrointestinal tract (USEPA 1987). Twenty percent of copper mist and dust is absorbed through inhalation (USEPA 1987).

Plasma copper content is subject to striking changes associated with the synthesis and release of ceruloplasmin, which is responsible for maintaining proper plasma copper concentrations, and is an essential transport protein in the metabolism of iron. Ceruloplasmin concentrations are elevated during pregnancy and with use of oral contraceptives, and appear to be affected by estrogen concentrations (Carruthers et al. 1966, as reported in NRC 1977, Gobler et al. 1953, Lahey et al. 1953, as reported in USEPA 1980).

The biological half-life of copper is very short. Most copper is excreted by the biliary system with additional amounts in sweat, urine, saliva, gastric and intestinal mucosae, and menstrual discharge (USEPA 1987).

Human homeostatic mechanisms help to control copper balance by regulating the absorption, storage, distribution, utilization and excretion of the metal. The population most sensitive to high copper levels is that suffering from Wilson's disease (~ 1 in 200,000 persons), in which an inborn error of metabolism produces increases in copper levels in all tissues. Newborns and small children are also more sensitive since they have underdeveloped homeostatic mechanisms (USEPA 1987).

G. Discussion - Derivation of Target Concentrations

Based on EPA's Carcinogen Risk Assessment guidelines there is insufficient data to determine the carcinogenic potential of copper to humans (USEPA 1987). The U.S. EPA has recommended an Acceptable Daily Intake (ADI) for copper of 3.7×10^{-2} mg/kg/day based on a human oral LOAEL of 7.6×10^{-2} mg/kg/day with an applied uncertainty factor of 2 (USEPA 1984, 1986). An ADI for inhalation

exposure of 1.0×10^{-2} mg/kg/day was also calculated based on a TLV of 1.0 mg/m^3 for copper mists and dusts with an applied uncertainty factor of 10 (ACGIH 1983 as reported in U.S. EPA 1984, 1986). ENVIRON has calculated an inhalation ADI of 3.0×10^{-2} mg/kg/day because the USEPA ADI is at or below the recommended daily allowance. The U.S. EPA has recommended a Maximum Contaminant Level (RCML) of water of 1.3 mg/1 based on a human oral LOAEL of 5.3 mg/day with a safety factor of 2 (USEPA 1985).

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Iron

CAS No.: 15438-31-0
Synonyms: ferrous iron

A. Physical and Chemical Properties

Chemical Formula:	Fe
Form:	silvery-white or gray, soft, ductile, malleable, somewhat magnetic metal; available as ingots, sheets, wire, or powder
Chemical Class:	metal
Atomic Weight:	55.86
Boiling Point:	3000°C
Melting Point:	1535°C
Specific Gravity:	7.86
Solubility in Water:	salts with various solubilities
Solubility in Organics:	NA
Organic Carbon Partition Coefficient:	NA
Log Octanol/Water Partition Coefficient:	NA
Vapor Pressure:	NA
Vapor Density:	NA
Henry's Law Constant:	NA
Bioconcentration Factor:	NA

B. Regulations and Standards

Safe Drinking Water Act
- Maximum Contaminant Level Goal (MCLG for Drinking Water (mg/L): NA
- Maximum Contaminant Level (MCL) for Drinking Water (mg/L): NA

Clean Water Act
- Ambient Water Quality Criteria (mg/L)
  - Human Health
    - Water and Fish Consumption: NA
    - Fish Consumption Only: NA
  - Aquatic Organisms (mg/L)
    - Fresh Water
      - Acute: NA
      - Chronic: NA

Marine
Acute: NA
Chronic: NA

References

Sax and Lewis 1987, Verschueren 1983, The Merck Index 1983, SPHEM 1986, EPA 1988

NA - Not Available

C. Fate and Transport

The major environmental fate processes for iron are sorption, hydrolysis, oxidation, chelation, and to a lesser extent bioaccumulation. Although iron is characterized by slow soil mobility, its rate of movement is dependent upon the soil chemistry (e.g., pH, ligands). In the aquatic environment iron is strongly hydrolyzed and also tends to chelate with other inorganic and organic substances. These organic and inorganic complexes become adsorbed on to sediment and are available for subsequent reintroduction into the water column. Similar to other metals, it appears that bioaccumulation is minimal in nekton (e.g., fish); however, filter feeders residing upon or in the sediments (e.g., mussels, clams) tend to accumulate high levels of metals. In natural waters iron availability is controlled by pH, concentration of ligands and chelators, and the redox environment. An additional fate mechanism is the oxidation of iron to the insoluble hydroxide. Based upon limited information, photolysis, volatilization, and degradation are considered to environmentally insignificant fate processes.

D. Ecotoxicology

Iron is a vital nutrient and has a low order of toxicity to land animals (NAS/NAE). Chickens fed 9000 mg/kg of iron developed phosphorus deficiency, but the deficiency was corrected by phosphorus supplements (NAS/NAE 1973)

Iron is not considered a drinking water problem to land animals because it precipitates out of solution before reaching toxic levels (NAS/NAE 1973).

The solubility of iron is strongly dependent on pH, redox potential and complexation (Hoover 1978). Most references deal with iron salts,

and most of these salts precipitate out, leaving little iron in solution (McKee & Wolf 1963).

Iron is also an essential nutrient for phytoplankton, but it must be present in a dissolved, organo complexed form to be utlized (Hoover 1978). Diatoms were destroyed, however, by flocculation and removed from the water column by settling iron particles (WPCA 1968).

The precipitation of iron may cause problems for benthic life and fish in both alkaline fresh water and salt water. Benthic organisms, fish, eggs, and aquatic plants may be smothered (NAS/NAE 1973). The iron precipitate may also irritate and coat the gills of fish and block respiration (NAS/NAE 1973). Sticklebacks were killed within five hours when exposed to 2500 mg Fe/L due to coating of the gills (McKee and Wolf 1963).

Aquatic toxicity depends on whether iron is present in the ferrous or ferric state, whether it is in suspension or solution, (McKee & WSolf 1963) and upon pH (NAS/NAE 1973).

Iron was toxic to carp at 0.9 mg/Fe/L at pH 5.5 and essentially nontoxic to carp at neutral pH (NAS/NAE 1973).

Iron methanoarsenate solution had a 48 hour LC50 value greater than 40 mg/L to Carp, goldfish, Medaka and Pond Loach (Spehar et al. 1982).

Brook trout 96 hour LC50 values for iron sulfate solutions were 0.41 mg/L, 0.48 mg/L, and 1.75 mg/L at pH 5.5, 6.0, and 7.0 respectively (Brungs, et al. 1977).

Ferric chloride was toxic to Daphnia magna within 48 hours at 21 mg/L (NAS/NAE 1973).

In seawater iron is not considered a problem because of its rapid precipitation (NAS/NAE 1973).

E. Human Toxicology

Iron is an essential element in the human diet. The major requirement for iron concerns hemoglobin formation, in which iron is the function core of the heme group. If iron is lacking in diet, or if ligands are present which compete for iron in formation of hemoglobin, a number of toxicities develop which are, essentially, anemias.

Although there is spurious literature which describes carcinogenicity for some iron salts (for example, $FeSO_4$), these results appear to be

due solely to mechanical effects (solid state carcinogenesis). Cancers in test animals arise only at injection sites, and by no other route of administration of iron salts. These data have no bearing on the human toxicity of iron.

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LEAD

GENERAL BACKGROUND INFORMATION

Lead is used extensively in the manufacture of storage batteries and was used in gasoline and paint. Lead is also a natural constituent of many soils, for which concentrations normally range from 10 to 30 mg lead per kilogram of soil (U.S. EPA, 1980).

PHARMACOKINETICS

Lead can be absorbed by the oral, inhalation or dermal exposure routes (see section on Relative Absorption Factors). Gastrointestinal absorption of lead varies considerably depending upon chemical form, dietary intake, and age (Forbes and Reina, 1974; Barltrop and Meek, 1975). The deposition and absorption of inhaled lead depends upon particle size, chemical form and the rate and depth of breathing (Randall et al., 1975; Nozaki, 1966; Chamberlain et al., 1975). Once absorbed, lead is distributed to the various organs of the body, with most distribution occurring into mineralized tissues (ATSDR, 1990). Placental transfer to the developing fetus is possible (Bellinger et al., 1987). Inorganic lead is not known to be biotransformed within the body. Absorbed lead is excreted via the urinary or fecal routes (ATSDR, 1990)

HUMAN TOXICOLOGICAL PROFILE

Cases of acute lead poisoning in humans are not common and have not been studied in experimental animals as thoroughly as chronic lead poisoning. Symptoms of acute lead poisoning from deliberate ingestion by humans may include vomiting, abdominal pain, hemolysis, liver damage, and reversible tubular necrosis (U.S. EPA, 1984). Subacute exposures in humans reportedly may produce a variety of neurological effects including dullness, restlessness, irritability, poor attention span, headaches, muscular tremor, hallucinations, and loss of memory. Nortier et al., (1980) report encephalopathy and renal damage to be the most serious complications of chronic toxicity in man and the hematopoietic system to be the most sensitive. For this reason, most data on the effects of lead exposure in humans are based upon blood lead levels. The effects of lead on the formation of hemoglobin and other hemoproteins, causing decreased levels, are reportedly detectable at lower levels of lead exposure than in any other organ system (Betts et al., 1973). Peripheral nerve dysfunction is observed in adults at levels of 30 to 50 μg/dL-blood. Children's nervous systems are reported to be affected at levels of 15 μg/dL-blood and higher (Benignus et al., 1981). In high doses, lead compounds may potentially cause abortions, premature delivery, and early membrane rupture (Rom, 1976).

MAMMALIAN TOXICOLOGICAL PROFILE

Acute oral lethal doses of lead in animals depend upon chemical form, but generally range from 500 to 30,000 mg/kg. Several reproduction studies on the effects of subchronic oral exposure to lead in rats have been conducted (Kimmel et al., 1976; Grant et al., 1980; Fowler et al., 1980). These studies report that lead acetate administered in drinking water at various concentrations caused depressed body weights at 50 and 250 mg-Pb/L water, histological changes in the kidneys of offspring, cytokaryomegaly of the tubular epithelial cells of the inner cortex at concentrations greater than or equal to 25 mg/L and postnatal developmental delays at 50 to 250 mg/L. Higher oral doses of lead may result in decreased fertility and fetotoxic effects in a variety of species (Hilderbrand et al., 1973). A reduction in the number of offspring of rats and mice exposed to 25 mg Pb/L drinking water with a chromium deficient diet was reported by Schroeder et al. (1970). Chronic oral exposure of female Long-Evans rats to lead (5 mg/PB/L-water) reportedly resulted in slight effects on tissue excitability, systolic blood pressure, and cardiac ATP concentrations (Kopp et al., 1980a,b).

GENOTOXICITY

Results of *in vitro* studies with human lymphocyte cultures using lead acetate were nearly equally positive and negative. Results of in vivo tests are also contradictory but suggest that lead may have an effect on chromosomes (sister chromatid exchange).
Results for gene mutations, DNA modification, and recombinations in various microorganisms using lead acetate, lead nitrate and lead chloride were consistently negative with or without metabolic activation. Lead chloride has been reported to inhibit both DNA and RNA synthesis. In *in vitro* mammalian test systems, lead acetate gave conflicting results.

No epidemiological data regarding the oral carcinogenic potential of lead could be located in the available literature. Chronic inhalation may result in a statistically significant increase in deaths due to tumors in the digestive organs and respiratory systems in lead smelter workers and battery plant workers (Kang et al., 1980). Several studies have reported tumor formation in experimental animals orally administered specific lead salts, not normally ingested by humans (Zawirska and Medras, 1972; Boyland et al., 1962; Ito, 1973). The carcinogenicity of inhaled lead in experimental animals could not be located in the available literature. The U.S. EPA has classified lead and lead compounds as Group B2 - Probable Human Carcinogens.

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MERCURY

GENERAL BACKGROUND INFORMATION

Mercury has been used in the past for medicinal purposes (Gosselin et al., 1984). There are a number of occupations associated with mercury exposure, particularly through inhalation. These include mining, smelting, chloralkali production, and the manufacture of mercury-containing products such as batteries, measuring devices (thermometers) and paints. Mercury has also been used agriculturally as a seed and cereal protectant and as a fungicide.

PHARMACOKINETICS

The pharmacokinetics and pharmacodynamics of mercury depend largely on its chemical form, organic, inorganic or elemental. Absorption efficiencies vary depending on route of exposure and chemical form (see section on Relative Absorption Factors). Distribution, metabolism and excretion depend largely on the lipid solubility, ionization state and molecular size of the specific chemical form (ATSDR, 1989).

HUMAN TOXICOLOGICAL PROFILE

Exposure to most forms of mercury is associated with a high degree of toxicity. Elemental (metallic) mercury causes behavioral effects and other nervous system damage. Inorganic mercury salts do not generally reach the brain, but will produce kidney damage. Divalent (mercuric) mercury is substantially more toxic in this regard than the monovalent (mercurous) form. Organic mercury compounds are also toxic. Symptoms of chronic mercury poisoning can be both neurological and psychological in nature as the central nervous system is the primary target organ. Hand and finger tremors, slurred or scanning speech patterns, and drunken, stupor-like (ataxic) gait are some motor-control impairments that have been observed in chronic mercurial toxicity. Visual disturbances may also occur, and the peripheral nervous system may be affected. A psychological syndrome known as erethism is know to occur. It is characterized by changes in behavior and personality including depression, fearfulness, restlessness, irritability, irascibility, timidity, indecision, and early embarrassment. Advanced cases may also experience memory loss, hallucination, and mental deterioration.

MAMMALIAN TOXICOLOGICAL PROFILE

In a study by Mitsumori et al. (1981), male and female mice were fed methyl mercury chloride in their diet for up to 78 weeks. Most of the high dose group died from neurotoxicity before the 26th week. Renal tumors developed in 13 of 16 males in the

intermediate dosage group by 53 weeks while only 1 male in the control group developed tumors. No renal tumors occurred in exposed or control females. Studies on rats have reported similar effects such as damage to kidneys and the peripheral nervous system (U.S. EPA, 1980). Mice treated with alkyl mercury phosphate were reported to have an increased frequency of offspring with cleft palates (Oharazawa, 1968) while mice treated with methylmercury had offspring with significantly lowered birth weights and possible neurological damage (Fujita, 1969). No adequate epidemiological studies exist on the teratogenic effects of methylmercury on humans (U.S. EPA, 1980).

GENOTOXICITY

Skerfving et al. (1974) reported a statistical relationship between chromosome breaks and concentrations of methyl mercury in the blood of Swedish subjects on fish diets. Concentrations were reported to be from 14-116 ng Hg/ml in the blood of exposed subjects and from 3-18 ng/ml in nonexposed subjects.

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NICKEL

GENERAL BACKGROUND INFORMATION

Nickel in the ambient atmosphere typically exists as a constituent of suspended particulate matter (U.S. EPA, 1985). The greatest volume of nickel emitted into the atmosphere is the result of fossil fuel combustion. Other sources of nickel emissions are primary production, incinerators, metallurgy, chemical manufacturing, cement manufacturing, coke ovens, nickel recovery, asbestos mining/milling and cooling towers.

PHARMACOKINETICS

Studies of nickel absorption have shown that it is absorbed by all routes of exposure to varying degrees, primarily dependent on the chemical form (see section on Relative Absorption Factors). Absorbed nickel is bound to serum components and distributed to body organs, reaching highest concentrations in kidney and lung tissue (Whanger, 1973). Nickel is not known to be biotransformed. Excretion of absorbed nickel is primarily through urine, with minor excretory routes through hair and sweat (ATSDR, 1988).

HUMAN TOXICOLOGICAL PROFILE

Nickel carbonyl $Ni(CO)_4$ is a particularly toxic form of nickel upon inhalation and causes chest pain, dry coughing, hyperpnea, cyanosis, occasional gastrointestinal symptoms, sweating, visual disturbances and severe weakness. This is often followed by pulmonary hemorrhage, edema and cellular derangement. Survivors may be left with pulmonary fibrosis. In the workplace, nickel dermatitis may result at high nickel concentrations. At lower concentrations some susceptible individuals develop eczema-like lesions. The threshold for these health effects is much greater than exposures which occur in the ambient environment. The major adverse effects of nickel in man are dermatitis, chemical pneumonitis, and lung and nasal cancers.

MAMMALIAN TOXICOLOGICAL PROFILE

Deaths occurred in rats and mice at concentrations greater than 3.3 and 1.7 mg/m^3 nickel, respectively, upon extended inhalation exposure to $NiSO_4$ (Dunnick et al., 1987). Mice exposed to Ni_3S_2 died due to necrotizing pneumonia at 7.3 mg/m^3 nickel (Benson et al., 1987). Prolonged exposure of hamsters to nickel oxide at 41.7 mg/m^3 resulted in decreased survival due to emphysema (Wehner et al., 1975). Oral LD_{50}s in rats vary depending upon the nickel-containing compound to which the rats were exposed. These range from 355 mg compound/kg (118 mg Ni/kg) for nickel acetate (Haro, 1968) to greater than 5000 mg

compound/kg for nickel oxide, nickel sulfide, and nickel subsulfide (Mastromatteo, 1986). Rats fed diets containing nickel sulfate hexahydrate at 0, 250, 500 and 1000 ppm nickel showed no adverse effects over three generations in fertility, gestation, viability or lactation.

GENOTOXICITY

Weak evidence exists for the mutagenicity of nickel in bacterial and mammalian cells. Nickel appears to induce chromosomal aberrations in cultured mammalian cells (Larramendy et al., 1981), but not in vivo (Waksvik and Boysen, 1982). Occupational studies of human exposure indicate that certain nickel compounds appear to be carcinogenic via inhalation. However, there is no evidence of carcinogenicity in mammals through ingestion or dermal exposure (U.S. EPA, 1985). Nickel subsulfide has been found to be carcinogenic via the inhalation route in rats (Ottolenghi et al., 1974). Studies on nickel exposure via the oral route are inadequate to reach conclusions on carcinogenicity (ATSDR, 1988).

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Selenium

CAS No.: 7782-49-2
Synonyms: NA

A. Physical and Chemical Properties

Chemical Formula:	Se
Form:	exists in several allotropic froms: amorphous, cryst or red, and gray or metallic
Chemical Class:	metal
Atomic Weight:	78.96
Boiling Point:	685°C
Melting Point:	range 200°C to 217°C
Specific Gravity:	range 4.26 to 4.81
Solubility in Water:	most forms insoluble
Solubility in Organics:	benzene, ether, carbon disulfide, methylene iodide
Organic Carbon Partition Coefficient:	NA
Log Octanol/Water Partition Coefficient:	NA
Vapor Pressure:	NA
Vapor Density:	NA
Henry's Law Constant:	NA
Bioconcentration Factor:	NA

B. Regulations and Standards

Safe Drinking Water Act
- Maximum Contaminant Level Goal (MCLG for Drinking Water (mg/L): 0.045
- Maximum Contaminant Level (MCL) for Drinking Water (mg/L): 0.01

Clean Water Act
- Ambient Water Quality Criteria (mg/L)
  - Human Health
    - Water and Fish Consumption: 1.00E-10
    - Fish Consumption Only: 1.00E-10
  - Aquatic Organisms (mg/L)
    - Fresh Water
      - Acute: 2.60E-01
      - Chronic: 3.50E-02

Marine
Acute: 4.10E-01
Chronic: 5.40E-02

References

Sax and Lewis 1987, Verschueren 1983, The Merck Index 1983, SPHEM 1986, EPA 1988

NA - Not Available

C. Fate and Transport

Sorption, biodegradation, and bioaccumulation of selenium in the environment are the most important fate processes. Most of the selenium in aquatic systems is probably transported as the dissolved species. There is a pronounced effect of pH on adsorption of selenium by clay minerals from landfill leachate. The biochemistry of selenium compounds has been well studied in terrestrial plants and animals encountered from the high selenium soils of the Rocky Mountain States. It appears that the conversion of selenium to inert and insoluble forms may occur in aquatic systems. Selenium is bioaccumulateed by a number of aquatic organisms and is strongly correlated with the concentration of mercury and other heavy metals in the organism. Selenium is an unusual compound; at low concentrations selenium is essential for a living organism's needs whereas high concentrations produce extreme toxicity. Volatilization, oxidation, photolysis and hydrolysis are not environmentally significant fate processes for selenium.

D. Ecotoxicology

Acute toxicity to freshwater aquatic life from inorganic selenate has been found to occur as low as 760 µg/l, and may occur at lower concentrations had more species been tested. Hence, the ambient water quality criterion for selenium has been set at 35 µg/l as a 24 hour average and not to exceed 260 µg/l at any time for protection of freshwater species (EPA, 1986). For saltwater species, this criterion has been set somewhat higher - 54 µg/l for a 24 hour average and excursions not to exceed 410 µg/l (EPA, 1986). Data concerning chronic toxicity of selenium to both freshwater and saltwater species is lacking.

Naturally-occurring selenium in groundwater has concentrated in some areas due to irrigation activities which allow residues to concentrate as water itself evaporates following surface application. These deposits have accumulated sufficiently in some parts of California to inhibit both plant and animal fecundity, essentially transformed poisoned sectors into barren landscape, devoid of any lifeforms.

E. Human Toxicology

Ironically, selenium is one of those enigmatic substances which at low doses appears to be anti-carcinogenic (and possibly essential), whereas at high doses it is carcinogenic. This metal, therefore, presents one of the most basic challenges to the linearized multi-stage no threshold model of carcinogenesis presently favored by regulatory agencies.

Since the selenium found at the site was associated with soil, the toxicology of inorganic selenium compounds other than hydrogen selenide will be considered relevant.

Selenium is an essential element where the margin of safety between "desirable" exposures and toxic levels is rather narrow. Deficiency in selenium will cause disturbances in the cellular protective defence mechanism against oxidative stress, where especially the role of selenium as a constituent in glutathione peroxidase has been discussed. Pathological signs of deficiency in mammals include inter alia liver necrosis and cardiomyopathy. The element has also been implicated as an anticarcinogen in several epidemiological and experimental studies.

The bioavailability of selenium is dependent on its chemical form; elemental selenium and selenides of heavy metals are very insoluble. Monogastric animals have a high intestinal absorption (more than 90% absorption of selenite in man) and is rapidly distributed in various organs. Some selenium compounds like selenium oxychloride are strong vesicants causing destruction of the skin and considerable dermal uptake. However, such compounds are not likely to be of interest in this context. Selenium may be biotransformed by methylation or incorporation in amino acids (e.g. Se-methionine). Dimethyl selenium is an intermediate in the formation of urinary trimethyl selenium which is exhaled (garlic breath) in acute

intoxication. Excretion is composed of a rapid phase of excretion of 15-40% of the absorbed dose during the first week, followed by a slow elimination with an approximate half-life of 100 days. Cumulative effects may, thus, be expected upon metabolic overloading.

Acute selenium poisoning in man is primarily characterized by toxic effects on the central nervous system which sometimes include convulsions. Inhalation of larger amounts of selenium dioxide may cause pulmonary edema.

Chronic intoxication gives rise to vague subjective symptoms like gastrointestinal stress, nervousness, lassitude as well as partial loss of hair and nails and discoloration of teeth. Evidence of chronic selenium intoxication by oral administration in man has been found in seleniferous areas. From chronic occupational over exposure liver and spleen damage as well as anemia have been described. In life stock ("alkali" disease) excess selenium in feed in the range of 25 ppm causes anorexia, loss of hair, atrophy of hooves, lameness, sterility, fatty necrosis of the liver, and anemia. Selenium has also caused embryotoxic as well as teratogenic effects.

In high doses selenium sulphides induce an increase in hepatocellular carcinomas and adenomas in male and female rats and female mice as well as pulmonary tumors in female mice. NTP has judged the animal evidence of carcinogenicity as sufficient. However, in this case the EPA has evidently taken the position that selenium may only pose a cancer risk at high doses or alternatively, that the rodent model is not valid here, and the compound is not listed as a carcinogen in the Superfund Public Health Evaluation Manual of October 1986. Selenium is consequently permitted as a feed additive in the US.

F. Discussion of Risk Assessment

The current drinking water standard (MCL) according to the Safe Drinking Water Act is set at 0.01 mg/L Considering available toxicological information as well as current work place standards, this value seems to be unduly conservative. Thus, the Federal standard for occupational exposure is given as 0.2 mg/m3 which implies that exposure to inorganic selenium at the TLV may give an absorption of about 0.06 mg/kg/day (assuming 50% absorption in the lungs). In line with this conclusion, the recent proposed recommended MCL has

been raised to 0.045 ug/L, giving a maximum daily intake of 0.09 mg, and in the Superfund Public Health Evaluation Manual of October 1986 oral AIS and AIC values are given as 0.003 mg/kg/day and the inhalation AIC value as 0.001 mg/kg/day.

G. References

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EPA (1986b) Superfund public health evaluation manual. Office of Emergency and Remedial Response, Washington, D.C.

SILVER

GENERAL BACKGROUND INFORMATION

Silver is used in photographic materials, batteries, paints and jewelry. Silver is used medically in dental amalgam and in medical supplies for burn treatment. Photographic materials are the major source of silver that is released into the environment. Trace amounts of silver are found in water from natural sources and industrial waste.

PHARMACOKINETICS

Studies in humans and animals indicate that silver compounds are absorbed readily by the inhalation and oral routes. Individuals and individual organs absorb silver selectively. The greatest concentrations are found in the reticuloendothelial organs. Silver undergoes oxidation and reduction reactions within the body and is excreted primarily via the fecal route (ATSDR, 1990).

HUMAN TOXICOLOGICAL PROFILE

Blue-gray discoloration of the skin has been observed in many individuals who have ingested metallic silver and silver compounds over periods of months to years. This condition is termed argyria. The pigmentation of the skin is primarily in sun-exposed areas. Silver-containing granules are also observed in the dermis. Gradual accumulation of 1 to 5 grams of silver will lead to generalized argyria. The discoloration is not known to be diagnostic of any other toxic effect (ATSDR, 1990). Occupational exposure to silver dusts can lead to respiratory and gastrointestinal irritation. The average air level was estimated to range from 0.039 to 0.378 mg/m^3. Duration of employment ranged from less than one year to greater than ten years. Symptoms included abdominal pain, sneezing, stuffiness, and sore throat. Granular deposits were also observed in the conjunctiva and corneas of the eyes (Rosenman et al., 1979; 1987). Medical case histories indicate that dermal exposure to silver and silver compounds for extended periods of time can lead to local skin discoloration similar in nature to the generalized pigmentation seen after repeated oral exposure. The amount of silver and the duration of exposure necessary to produce this effect have not been established (McMahon and Bergfeld, 1983).

MAMMALIAN TOXICOLOGICAL PROFILE

Oral doses of 1,680 mg/kg silver colloid resulted in the deaths of rats after four days (Dequidt et al., 1974). Ingestion of silver nitrate and silver chloride will also cause deposition of silver granules in the skin of animals (Walker, 1971). Granules were observed in the eyes

of rats exposed to silver nitrate in drinking water at doses of 222 mg/kg/day over 37 weeks. These doses also cause general deposition in other tissues (Matuk et al., 1981). Mice given oral doses of 18.1 mg/kg/day silver nitrate for 125 days were observed to have silver deposits in their nervous systems. These animals were less active than unexposed controls (Rungby and Danscher, 1984). Silver has been found in the brains of neonatal rats whose mothers received silver lactate on days 18 and 19 of gestation (Rungby and Danscher, 1984). No studies were located that examine the reproductive effects of silver in animals or humans.

GENOTOXICITY

Silver is not mutagenic in bacteria but it has been found to cause DNA damage in mammalian cell culture (Robinson et al., 1982). No studies were located regarding cancer in humans or animals following oral, inhalation or dermal exposure to silver or silver compounds (ATSDR, 1990).

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THALLIUM

GENERAL BACKGROUND INFORMATION

Pure thallium is a soft bluish-white metal that is widely distributed in trace amount in the earth's crust. It is used in the manufacture of electronic devices, switches, and closures. It is also used to a limited extent in the manufacture of special glasses and for medical procedures that evaluate heart disease. Up until 1972, thallium was also used as a rat poison (ATSDR, 1991).

PHARMACOKINETICS

Thallium appears to be nearly completely absorbed from the gastrointestinal tract. No information was located on absorption following inhalation or dermal exposure. However, animal studies following intratracheal administration suggested that uptake through respiratory epithelium was rapid and complete. There is little information on the distribution of thallium in humans. Analysis of human tissues indicates that thallium is distributed throughout the body. The highest levels were found in the scalp hair, kidney, heart, bone, and spleen. In animals, the highest levels are found in the kidneys and liver. Excretion of thallium occurs by both the urinary and fecal routes (ATSDR, 1991).

HUMAN TOXICOLOGICAL PROFILE

Thallium is acutely lethal to humans following oral exposure at doses of 54-110 mg thallium/kg of body weight as thallium sulfate (Davis et al., 1981). The estimated lethal dose is approximately 14-15 mg/kg (Gosselin et al., 1984). Thallium compounds can affect the respiratory, cardiovascular, and gastrointestinal systems, the liver, kidneys and the male reproductive system. Alopecia (hair loss) and changes in the nervous system are characteristic of thallium exposure. A retrospective study was conducted which compared the incidence of congenital abnormalities in children born to mothers who had been exposed to thallium during pregnancy (Dolgner et al., 1983). The number of anomalies in the exposed group did not exceed the number of expected birth defects in the general population.

MAMMALIAN TOXICOLOGICAL PROFILE

In animals, the lowest doses showing lethality for a brief exposure period ranged from 5 to 30 mg/kg body weight for several species (Downs et al., 1960). Exposure to low doses (1.4 mg thallium as thallium sulfate/kg body weight/day) for longer durations (40-240 days) also cause death (Manzo et al., 1983). Electromyographic abnormalities without changes in

the myocardium are seem following a single oral dose (56 mg thallium/kg as thallium sulfate) in rabbits (Grunfeld et al., 1963). Parenteral injection in animals has been observed to cause liver effects. Thallium did not cause renal effects in rats following oral exposure, but parenteral exposure studies demonstrated that thallium affects the kidneys following subcutaneous administration. Rats exposed prenatally to 0.08 mg thallium/kg/day or greater during gestation evidenced impairment of learning. These effects occurred at dose levels below those at which other neurological effects (e.g structural and functional alterations of peripheral nerves) have been observed. Cultured rat embryos exposed to thallium at concentrations of 10, 30, or 100 ug/ml showed dose-related growth retardation at all levels showing embyrotoxic effects (Anschutz et al., 1981). Administration by intraperitoneal injection to pregnant rats at a dose of 2.0 mg thallium/kg/day (as thallium sulfate) during gestation days 8-10 resulted in reduced fetal body weights, hydronephrosis, and the absence of vertebral bodies (Gibson and Becker, 1970).

GENOTOXICITY

Animal and bacterial assays suggest than thallium is genotoxic. Thallium-induced dominant lethal mutations in male rats in vivo. The overall embryonic mortality increased at doses of 0.04 ug thallium/kg day or greater as thallium carbonate. In vitro DNA damage tests employing rat embryo cells were positive (Zasukhina et al., 1983). Thallium enhanced viral-induced transformations in Syrian hamster embryo cells (Casto et al., 1979) and was positive in bacterial assays (Kanematsu et al., 1980). No studies are available on the carcinogenic effects of inhalation, oral or dermal exposure to thallium.

REFERENCES

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Tin

CAS No.: 7440-31-5
Synonyms: NA

A. Physical and Chemical Properties

Chemical Formula:	Sn
Form:	almost silver-white, lustrous, soft, very malleable and ductile metal; easily powdered; available in bars, foil, shot, powder, etc.
Chemical Class:	Metal
Atomic Weight:	118.69
Boiling Point:	2507°C
Melting Point:	231.9°C
Specific Gravity:	7.31
Solubility in Water:	insoluble, some salts are soluble
Solubility in Organics:	NA
Organic Carbon Partition Coefficient:	NA
Log Octanol/Water Partition Coefficient:	NA
Vapor Pressure:	0
Vapor Density:	0
Henry's Law Constant:	0
Bioconcentration Factor:	

B. Regulations and Standards

Safe Drinking Water Act
Maximum Contaminant Level Goal (MCLG for Drinking Water (mg/L): NA

Maximum Contaminant Level (MCL) for Drinking Water (mg/L): NA

Clean Water Act
Ambient Water Quality Criteria (mg/L)
Human Health
Water and Fish Consumption: NA
Fish Consumption Only: NA

Aquatic Organisms (mg/L)
Fresh Water
Acute: NA
Chronic: NA
Marine
Acute: NA
Chronic: NA

References

Sax and Lewis 1987, Verschueren 1983, The Merck Index 1983, SPHEM 1986, EPA 1988

NA - Not Available

C. Ecotoxicology

Data regarding the ecotoxic properties of tin is presently lacking. Tin does not occur naturally in the aquatic environment and any inputs to natural systems would be anthropogenic.

Tin would probably behave similar to lead in natural systems; however, its ecotoxicity can not be assumed to resemble lead. Although no studies were identified that indicate an acute sensitivity of aquatic organisms, marine species appear to be more sensitive than their freshwater counterparts.

D. Human Toxicology

Inorganic tin has not been found to be carcinogenic or teratogenic in humans or animals. At high doses tin salts are toxic when they gain access to the blood stream, producing paralysis, neurologic and kidney damage, and liver dysfunction. At low oral doses, adverse effects in humans include gastrointestinal irritation and vomiting. Inorganic tin is poorly absorbed from the gastrointestinal tract and exposure to a toxic does seems unlikely in most cases. An oral ADI of 3.3×10^{-2} mg/kg/day has been calculated based on a subchronic animal study (De Groot et al. 1973).

- **Acute and Chronic Toxicology**

There is no experimental evidence indicating that any of the inorganic tin compounds are carcinogenic or teratogenic (WHO 1980). A recent two year feeding study in rats and mice indicated that doses of 1,000 and 2,000 ppm stannous chloride did not cause a statistically

significant increase in tumors (NTP 1982). WHO also notes three studies investigating the possible carcinogenic effects of inorganic tin salts in rats and mice; none of the studies observed a dose-dependent increase in tumors in the treated animals. There is one report indicating that tin (II) chloride might have an effect on the reproductive system. De Groot et al. (1973) noted moderate testicular degeneration in rats after feeding for 13 weeks with a diet containing 1% stannous chloride (220-330 mg/kg/day).

Although tin is present in small amounts in most animal and human tissues it is uncertain whether it is an essential element for mammals. Some results, however, do indicate that it is an essential nutrient for the growth of the rat (WHO 1980). One report by Schwartz et al. (1970) states that the growth rate of rats was enhanced 60% when 1-2 ppm tin as tin sulfate was added to a highly purified diet.

There is no known evidence of chronic toxicity stemming from oral exposure to inorganic tin in humans. In general, soluble tin salts are acute gastrointestinal irritants, which explains the severe diarrhea and other acute local effects observed in man and animals after consumption of food with high concentrations (1370 ppm or more) of inorganic tin (Benoy et al. 1971). In animals, high doses (10 g/kg diet) of inorganic compounds seem to affect the central nervous system producing such effects as ataxia, muscular weakness, and the depression of the central nervous system, as well as testicular degeneration (De Groot et al. 1973). High doses of inorganic tin also cause kidney damage, affect liver functions, and possible interfere with hemoglobin formation (WHO 1980).

In summary, since there is little human evidence of long-term toxic effects stemming from chronic exposure to inorganic tin, it is difficult to quantify an ADI. The human exposure data base consists mostly of cases reports of outbreaks of gastroenteritis associated with exposure to a single high does of inorganic tin; moreover, there is no evidence to indicate the effects were due to the absorption of tin. Rather, the likeliest cause of gastroenteritis is local irritation of the mucous membranes of the alimentary tract (WHO 1980). In general, studies suggest that individuals may display one-time acute nausea and/or gastroenteritis after exposure to inorganic tin in the range of 250-500 mg/kg in juice. Benoy et a. (1971) observed nausea and gastroenteritis in 5 volunteers after exposure to 5-7 mg/kg bw of fruit juice containing tin concentrations of about 1400 mg/l as a single dose, but no effects were noted at lower doses. In another study no effects were seen in human volunteers when they were fed for 24 days on canned food with a tin content of 200 mg/kg (Calloway and McMullen 1966). Thus, there appears to be a wide range in sensitivities, and the relatively low "safe levels" may be explained, in part, by the mechanism

proposed by De Groot (1973) and clarified by Greger and Johnson (1982) where, in rats, tin exerts its effect on the intestinal lumen by inhibiting the absorption of dietary calcium and zinc. The appended table summarizes the effects noted in the most important human and animal studies.

E. Pharmacokinetics

Evidence from man and several animal studies shows that inorganic tin is poorly absorbed from the gastrointestinal tract (WHO 1980). Estimates based on studies with rats show that 2.8% of tin (II) and 0.6% of tin (IV) were absorbed after oral dosing (Hiles 1974). Furchner and Drake (1976) found no species differences in the gastrointestinal absorption of tin (II) and gave 5% as a conservative estimate of gut absorption in mice, rats, dogs, and monkeys. In man, the apparent tin absorption was 3.1% from a diet supplemented with 50 mg tin, though when intake was reduced to 0.2 mg per day the absorbed proportion significantly increased (Johnson and Greger 1982). Thus for the purposes of this risk assessment it is assumed that, as a conservative estimate of gastrointestinal absorption, 10% of an oral dose of inorganic tin would be absorbed, based on the combined results of the above studies.

With both oral and parental administration of tin to animals, the highest concentration were found in the kidney, liver and bone, with bone being the principal site of deposition (Furcher and Drake 1976). Schroeder et al. (1964) reported a highly variable distribution of tin in human tissues with significant differences related to age and geographical location (range 0-34 mg.kg dry weight in the kidney). The major route of excretion of absorbed inorganic tin is the kidney, although a small fraction is excreted into the bile (WHO 1980).

F. Discussion - Derivation of Target Concentrations

The no-observed-effect dietary level (NOEL) for inorganic tin appears to be 1 g stannous chloride/kg (22-33 mg.Sn/kg bw/day--if the diet is supplemented with iron) based on the 90 day study by De Groot et al. (1973). Similarly no effect on growth was observed by Conine et al. (1976) when sodium pentafluorostannite was administered orally to rats at a dose rate of 20 mg/kg/day for 30 days. Using 33 mg/kg/day as the NOEL and a safety factor of 1000, ENVIRON has calculated an ADI for inorganic tin as 0.033 mg/kg/day.

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INORGANIC TIN ORAL STUDIES

Ref	Species	Dose/ Duration	LOEL (mg/kg/day)	NOEL (mg/kg/day)	Comments
Roe et al. (1965)	Rat	Tin (II) ethyl hexanoate and $NaSnC_{15}$ for 1 year	---	300-600	as compound
Conine et al. (1976)	Rat	$NaSnF_5$ for 30 days	100	20	as tin
De Groot et al. (1973)	Rat	$SnC12^*H_2O$ and	66-99	22-33	as tin
		Sn O for 13 weeks	66--99	22-33	as tin
Benoy et al. (1971)	Rat	Drank juices with high tin levels for 24 hours.	---	130-190	as tin
	Cat	Single dose; juice with tin	10.0	6.85	as tin
	Dog		---	6.58-7.59	as tin
	Humans	Single does; juice with tin	4.38-6.71	1.73-2.65	as tin
Calloway & McMullen (1966)	Humans	Tin from canned food	9 days	33	as tin
	Humans		24 days	204	as tin

ZINC

GENERAL BACKGROUND INFORMATION

Zinc is used most commonly as a protective coating for other metals and in alloys such as bronze and brass. Zinc is emitted to the atmosphere during mining and refining, manufacturing processes, and combustion of zinc-containing materials. Zinc is an essential trace element in nutrition and is found in many foods (ATSDR, 1989).

PHARMACOKINETICS

It has been reported that about 20 to 30 percent of ingested zinc is absorbed and the mechanism may be homeostatically controlled and carrier-mediated. When zinc levels in the body are sufficient to sustain normal physiological functions, zinc absorption decreases. Absorption occurs by the inhalation and dermal routes as well. Once absorbed, zinc is distributed throughout the body where it is used as an essential cofactor in many enzyme systems. Excretion occurs primarily through the feces (ATSDR, 1989).

HUMAN TOXICOLOGICAL PROFILE

Zinc compounds are of relatively low toxicity by ingestion. In humans, exposure to 2 g or more of zinc produces symptoms of fever, nausea, vomiting, stomach cramps, and diarrhea 3-12 hours after ingestion. Zinc chloride is a primary component of smoke bombs, and pathologic changes in humans due to acute inhalation exposure to ZnCl include laryngeal, tracheal, and bronchial mucosal edema and ulceration, interstitial edema, interstitial fibrosis, alveolar obliteration and bronchiolitis obliterans. Severe acute injury is associated with a high mortality (Matarese and Matthews, 1986). Metal fume fever results from occupational inhalation of freshly formed fumes of zinc oxides. It is characterized by transient chills and fever, profuse sweating, and weakness some hours after exposure. The fumes usually consist of extremely fine particles containing other metals in addition to zinc. The very small size (submicronic) of the fume particles with their potential for alveolar deposition is thought to be an important aspect of this phenomenon. It has generally been estimated that fume fever does not occur at zinc oxide levels less than 15 mg/m^3 although some occurrence of fume fever has been reported at levels as low as 5 mg/m^3. This occupational hazard is not considered to be a general public health problem (U.S. EPA, 1987a; U.S. EPA, 1987b). Poorly ionized zinc compounds have low dermal toxicity and have been used therapeutically and cosmetically for many years as mild astringents, antiseptics and perspirants (Gilman et al., 1985).

MAMMALIAN TOXICOLOGICAL PROFILE

The highly ionizable zinc salts such as zinc chloride can be acutely toxic. Acute toxicity in laboratory animals was reported to be 250 mg/kg (LD_{Lo}) for the guinea pig. A TC_{Lo} of 4800 mg/m^3 for 30 minutes was calculated for humans (Clayton and Clayton, 1981).

Zinc has a low oral chronic toxicity. In a study involving dogs and cats, 175 to 1000 mg/kg per day of ZnO, administered orally for 3 to 53 weeks, was tolerated. Some of the dogs showed glucosuria and some of the cats showed fibrous degeneration of the pancreas. A number of other animal feeding studies demonstrate the low oral toxicity of zinc (Clayton and Clayton, 1981; U.S. EPA, 1987a).

Generally adverse but minor effects have been demonstrated in guinea pigs inhaling large amounts (1-5 mg/m^3) of zinc oxides (Lam et al., 1982,1985; Amdur et al., 1982). Lam et al. (1985) measured pulmonary function in guinea pigs exposed to zinc oxide fume at 5 mg/m^3 three hours daily for a period of six days. Vital capacity, functional residual capacity, alveolar volume, and single breath diffusive capacity for carbon monoxide decreased following the final exposure and did not return to normal after 72 hours. Flow resistance increases, and decreases in compliance and total lung capacity returned to normal after this period. Fibroblasts in interstitial infiltrates (including a fibrotic reaction) were observed. It was concluded that pulmonary changes may occur with relatively few exposures at the workplace threshold limit value.

Zinc does not appear to be teratogenic except perhaps at very high doses; intraperitoneal injections of relatively large doses (20 mg/kg) in mice during pregnancy results in some malformations in fetal ossifications (Chang et al., 1977).

GENOTOXICITY

Various studies have indicated that zinc is not mutagenic. In vitro analyses of zinc chloride demonstrated that the fidelity of DNA synthesis was unaffected (Sirover and Loeb, 1976a,b; Miyaki et al., 1977). Zinc industry employees have shown a greater number of chromosomal aberrations in peripheral blood lymphocytes than did controls (Bauchinger et al., 1976). However, these workers were also exposed to other agents known to cause chromosome structural alterations (Leonard, 1985). There is no evidence that the inhalation, ingestion or parenteral administration of zinc induces the formation of tumors.

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