APPENDIX H

Toxicological Profiles

APPENDIX H1

Human Health Toxicological Profiles

Antimony

Arsenic

Cadmium

Chloroform

Chromium

Copper

Bromodichloromethane

Di-n-butylphthalate

Ethylbenzene

Lead

Mercury

Methylene chloride

Nickel

Silver

Tetrachloroethene

Toluene

Trichloroethene

Trichlorofluoromethane

1,1,2-Trichloro-1,2,2-Trifluoroethane

2,4,6-Trinitrotoluene

Vanadium

Xylenes

Zinc

H.1.1 Antimony

H.1.1.1 Occurrence and Use

Antimony (Sb) is a naturally occurring metal found in a tri- or pentavalent state. Antimony is frequently associated with sulfide and sulfide ores (Carson et al., 1986). Antimony and compounds are primarily used in the production of lead, copper and other metal alloys, as well as commercially in fireproofing textiles, ceramics, glassware, pigments, and in antiparasitic drugs (Carson et al., 1986). Antimony is a common industrial air pollutant, but the general public is largely exposed to antimony from food (Goyer, 1986).

Soil antimony concentrations typically range from 0.1 to 10 mg/kg (dry weight) (Elinder and Friberg, 1986). Air concentrations in the Chicago area have ranged between 1.4 to 55 ng/m^3, with a mean of 32 ng/m^3.

H.1.1.2 Physical and Chemical Properties of Antimony

Molecular Weight	122.00
Water Solubility, mg/l	0.0E+00
Bioaccumulation Factor for Fish	1.0E+00
Bioaccumulation Factor for Shellfish	1.0E+01

Source: Multi-Media Exposure Assessment Manual, 1989

H.1.1.3 Environmental Fate and Transport

Various forms of antimony found in the environment from natural and anthropogenic sources undergo a complex cycle of chemical interconversion and transfer between media. antimony in water may undergo either oxidation or reduction, depending on pH and other ions present. Soluble forms of Sb (e.g., antimony potassium oxalate and antimony potassium tartrate) tend to by quite mobile in water, while less soluble species adsorb to clay or soil particles (Callahan et al., 1979).

Antimony in gaseous, vapor and particulate forms enters the atmosphere and is transported via air until it undergoes atmospheric fallout or washout and is deposited in oceans, estuaries, lakes, rivers, sediments and terrestrial systems. Antimony may enter the food chain via root uptake by terrestrial plants and via bioaccumulation in fish- and plant-eating mammals. Antimony deposited in sediment can also be released to the atmosphere through microbial activity under anaerobic conditions. Antimony may leach from municipal landfills, sewage sludge, oil-fired plant incinerator ash and fertilizers to contaminate ground water, surface water and sediment (Callahan et al., 1979).

H.1.1.4 Routes of Exposure, Distribution, Absorption, Transport and Degradation

According to EPA (1989), multimedia antimony exposures are essentially negligible by comparison to occupational exposures at which discrete clinical health effects have been observed. Myocardial effects are among the best-characterized human health effects associated with antimony exposure.

Quantitative estimates on the efficiency of pulmonary absorption of antimony are not available, but Elinder and Friberg (1986) state that trivalent antimony is absorbed from the lungs to a large extent. Absorption from the gastrointestinal (GI) trace is slow and it has been reported that at least 15 percent of a single oral dose of antimony potassium tartrate was absorbed by mice (Waitz et al., 1965). Once absorbed, the highest concentrations are found in the thyroid, adrenals, liver, heart and kidneys (Carson et al., 1986). Elimination of antimony is somewhat rapid depending on route and valence state but occurs via both feces and urine. The typical human daily intake of antimony, from all sources ranges between 10 and 1250 μg (Elinder and Friberg, 1986).

H.1.1.5 Acute Toxicity

The primary effect of acute antimony exposure is direct irritation of tissues (Sittig, 1985). Acute inhalation exposures elicited an irritative effect on the upper respiratory tract of workers exposed to 73 mg/m^3 antimony trichloride (Elinder and Friberg, 1986) Exposes to high levels of antimony fumes are capab.e of producing GI effects of abdominal cramps, diarrhea, and vomiting

(Carson et al., 1986). In severe cases, pulmonary edema and even death have been seen in exposed workers. Other effects seen are rhinitis (nasal mucous irritation) and skin irritation, which may lead to lesions in moist exposed areas of the body (Sittig, 1985). Experimental animals administered an intravenous injection of antimony displayed circulatory and cardiac alterations (Carson et al., 1986).

H.1.1.6 Chronic Toxicity

Antimony tends to accumulate in the lung following inhalation exposures where chronic respiratory tract symptoms of pharyngitis and tracheitis are seen (Goyer, 1986). If exposures persist, these irritation systems may progress to bronchitis, pneumoconiosis, obstructive pulmonary disease, and emphysema (Goyer, 1986). These pulmonary effects can be observed visually as changes in chest x-rays (characterized by densely distributed opacities (Elinder and Friberg, 1986). Chronic occupational exposures to antimony trioxide have been associated with heart disease with occasional fatalities (Carson et al., 1986). Pustular skin eruptions ("antimony spots") in exposed workers are sometimes seen in employees working with antimony compounds (Elinder and Friberg, 1986). For years antimony was used in anti-parasitic therapy (principally for schistosomiasis) where some of the above side effects were noted as well as elevation of liver enzymes (GOT and GPOT) in some patients at the early stages of therapy (Elinder and Friberg, 1986).

H.1.1.7 Mutagenicity, Carcinogenicity and Teratogenicity

Mutagenicity

Several antimony compounds were found to be mutagenic in Bacillus subtillus (Carson et al., 1986). Increased chromosomal defects were observed in human lymphocytes and Syrian hamster embryo cells incubated in antimony compounds (Paton and Allison, 1975; Casto et al., 1979).

Carcinogenicity

There is very little data on possible human carcinogenicity of antimony compounds. The American Conference of Governmental Industrial Hygienists (ACGIH) concluded in 1983 that antimony oxide should be regarded as a suspected carcinogen based on unpublished data obtained

from a large antimony smelter in the U.K. which showed an increased incidence of mortality from lung cancer in heavily exposed workers (ACGIH, 1983). However, Elinder and Friberg (1986) state that in this study other chemical exposures occurred which make interpretation of this data from the U.K. difficult. In addition, a high frequency of lung neoplasias was observed in rats exposed to airborne antimony at a concentration of 4.2 mg/m^3 (Watt, 1983), while oral dosing of rats has not produced any excess of tumors (Goyer, 1986). Antimony has not been evaluated by the EPA for carcinogenicity, therefore a carcinogenic classification has not been determined (USEPA, 1989a).

Teratogenicity (and other reproductive effects)

A 1967 Russian study reported an 8 percent increase of spontaneous late abortions in female antimony smelter workers compared to an unexposed population control (Carson et al., 1986). Infant weights from exposed mothers were not birth differential but were significantly lower when measured at one year. Other studies have reported a slight increase in premature deliveries for female antimony workers exposed during pregnancy (Carson et al., 1986). Experimental animals have experienced uterine and ovarian disorders when exposed to antimony, but no cases of fetal malformation have been reported in pregnant rats exposed to 125 or 250 mg/kg antimony (route unknown) (Carson et al., 1986).

H.1.1.8 EPA Carcinogenic Classification and Dose-Response Parameters

The following dose-response parameters and discussions were extracted from IRIS, 1994.

EPA Carcinogenic Classification

The EPA has not classified Antimony in terms of carcinogenicity, and no cancer dose-response parameters have been derived.

Dose Response Parameters (IRIS, 1994)

Carcinogenic Effects: No data

Noncarcinogenic Effects:

ORAL RfD SUMMARY :

RfD: 4E-04 mg/kg/day

STUDY USED TO DERIVE RfD: Shroeder, H.A., M. Mitchner and A.P. Nasor. 1970. Zirconium, niobium, antimony, vanadium and lead in rats: Life term studies. J. Nutrition. 100:59-66.

ORAL RfD UNCERTAINTY :

UF = 1000. An uncertainty factor of 1000 (10 for interspecies conversion, 10 to protect sensitive individuals, and 10 because the effect level was a LOAEL and no NOEL was established) was applied to the LOAEL of 0.35 mg/kg bw/day.

ORAL RfD MODIFYING FACTOR:

MF = 1.

ORAL RfD CONFIDENCE :

Study: Low

Data Base: Low

RfD: Low

Confidence in the chosen study is rated as low because only one species was used, only one dose level was used, no NOEL was determined, and gross pathology and histopathology were not well described. Confidence in the data base is low due to lack of adequate oral exposure investigations. Low confidence in the RfD follows.

H.1.1.9 References

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H.1.2 Arsenic

H.1.2.1 Occurrence and Use

Arsenic is a component of manufactured metal alloys, electrical devices, glass, wood preservatives, agricultural chemicals, and is also used as a therapeutic agent. The element is distributed widely in natural soils; typical concentrations is U.S. soils have been found to be between >1 and about 30 mg/kg (Kabata-Pendias and Pendias, 1987). Most arsenic releases to the environment occur as byproducts of metal smelting and refining activities.

H.1.2.2 Physical and Chemical Properties of Arsenic

Molecular Weight	75.00[1]
Water Solubility, mg/l	0.0E+00[2]
Vapor Pressure, mm Hg	0.0E+OO[3]
Bioaccumulation Factor for Fish	1.0E+00[4]
Bioaccumulation Factor for Shellfish	4.0E+00[5]

Sources: [1]Multi-Media Exposure Assessment Manual, 1989

[2]Weast, 1979

[3]EPA, 1981

[4]Spehar et al., 1980

[5]Strenge et al., 1986

H.1.2.3 Environmental Fate and Transport

In the natural environment arsenic has four different oxidation states;chemical speciation is important in determining arsenic's distribution and mobility. Interconversions of the +3 and +5 states as will as organic complexation do occur and can be mediated by microorganisms. Arsenic is generally quite mobile in the environment and is mainly transported by water (WHO, 1981). In oxygenated water, arsenic usually occurs as arsenate, but under reducing conditions (i.e., deep will waters) arsenite predominates. In the aquatic environment, volatilization is important when biological activity or highly reducing conditions produce arsine of methyl-arsenics.

Sedimentation of arsenic in association with iron and aluminum does occur frequently (WHO, 1981).

Significant sources of As in soils are related to industrial activities such as metal processing, coal combustion, geothermal power production, and to the use of arsenical herbicides. The reactions of As in soils are highly governed by its oxidized state. However, arsenate ions are known to be readily fixed by such soil components as clays, phosphatic gels, humus, and calcium, and the most active in As retention are hydrated Fe and Al oxides. In oxygenated soil, inorganic arsenic is prevalent in the pentavalent (+5) form. Under reducing conditions, the trivalent form predominated (WHO, 1981). Hydroxy-Al on the external surfaces of micaceous minerals is reported to be especially significant in the retention of As. The mobility of As in soil was shown to be proportional to the As added and inversely proportional to time and to Fe and Al contents. The toxicity of As depends on the concentration of soluble As, therefore, sodium arsenate and arsenic trioxide, formerly used as herbicides, are the most toxic (Kabata-Pendias and Pendias, 1987).

H.1.2.4 Routes of Exposure, Distribution, Absorption, Transport, and Degradation

Arsenic is readily absorbed via the oral and inhalation routes. Both inorganic and organic forms of arsenic are readily absorbed from the gastrointestinal tract with the more soluble forms being more readily absorbed than the insoluble forms (USEPA, 1984). Approximately 95 percent of soluble inorganic arsenic administered to rats is absorbed from the gastrointestinal tract (Coulson et al., 1935; Ray-Bettley and O'Shea, 1975). The USEPA (1984) assumes that, on the average, 70-80 percent of arsenic is absorbed in the respiratory tract. Dermal absorption is not significant (USEPA, 1984).

H.1.2.5 Acute Toxicity

Acute exposure of humans to high levels (71 mg/kg) of metalloid arsenic has been associated with gastrointestinal effects, hemolysis, and neuropathy.

H.1.2.6 Chronic Toxicity

Chronic exposure of humans to arsenic can produce toxic effects on both the peripheral and central nervous systems, keratosis, hyperpigmentation, precancerous dermal lesions and cardiovascular damage (USEPA, 1984).

H.1.2.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Current existing evidence suggests that arsenic is mutagenic. Although bioassays of laboratory animals have not as yet revealed an ability to arsenic to cause chromosome aberrations, some studies suggest that humans exposed to arsenic exhibit elevated frequencies of sister chromatid exchanges and chromosome aberrations. Arsenic may be substituted for phosphorus in the DNA backbone, and may inhibit DNA repair mechanisms (ATSDR, 1989)

Carcinogenicity

Arsenic is a known human carcinogen. Epidemiological studies of workers in smelters and in plants manufacturing arsenical pesticides have shown that inhalation of arsenic is strongly associated with lung cancer and perhaps with hepatic angiosarcoma (USEPA, 1984). Ingestion of arsenic has been linked to a form of skin cancer and more recently to bladder, liver and lung cancers (Tseng et al., 1968; Chen et al., 1986).

Teratogenicity (and other reproductive effects)

Arsenic is embryotoxic, fetotoxic, and teratogenic in several animal species (USEPA, 1984).

H.1.2.8 Carcinogenic Classification and EPA Dose-Response Parameters

The following dose-response parameters and discussions were extracted from IRIS, 1994.

EPA Carcinogenic Classification

Arsenic is classified as a known human carcinogen (Group A). This classification is based on observation of increased lung cancer mortality in populations exposed primarily through inhala-

tion and on increased skin cancer incidence in several populations consuming drinking water with high arsenic concentrations.

Dose-Response Parameters (IRIS, 1994)

Carcinogenic Effects:

INHALATION UNIT RISK: 4.3E-3/µg/cu.m

INGESTION UNIT RISK: 1.75 mg/kg/day

Noncarcinogenic Effects:

ORAL RfD SUMMARY :

RfD: 3E-4 mg/kg/day

Critical effect: keratosis, hyperpigmentation, and possible vascular complications.

NOTE: There was not a clear consensus among Agency scientists on the oral RfD. Applying the Agency's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 µg/kg/day. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the Work Group as it becomes available. Risk managers should recognize the considerable flexibility afforded them in formulating regulatory decisions when uncertainty and lack of clear consensus are taken into account.

Conversion Factors: NOAEL was based on an arithmetic mean of 0.009 mg/L in a range of arsenic concentration of 0.001 to 0.017 mg/L. This NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg bw (Abernathy et al., 1989). NOAEL = [(0.009 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.0008 mg/kg/day. The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng

(1977) of 0.17 mg/L. LOAEL = [(0.17 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.014 mg/kg/day.

ORAL RfD UNCERTAINTY :

UF = 3. The UF of 3 is to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals.

ORAL RfD MODIFYING FACTOR :

MF = 1.

ORAL RfD CONFIDENCE :

Study: Medium

Data Base: Medium

RfD: Medium

Confidence in the chosen study is considered medium. An extremely large number of people were included in the assessment (>40,000) but the doses were not well-characterized and other contaminants were present. The supporting human toxicity data base is extensive but somewhat flawed. Problems exist with all of the epidemiological studies. For example, the Tseng studies do not look at potential exposure from food or other source. A similar criticism can be made of the Cebrian et al. (1983) study. The U.S. studies are too small in number to resolve several issues. However, the data base does support the choice of NOAEL. It garners medium confidence. Medium confidence in the RfD follows.

H.1.2.9 References

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H.1.3 Cadmium

H.1.3.1 Occurrence and Use

Cadmium (Cd) is a noncorrosive metal used in a wide variety of industrial processes, such as electroplating and galvanizing, and is a byproduct of zinc and lead mining. It is also used as a color pigment for paints and plastics, and cathode material for nickel-cadmium batteries. The combustion of fossil fuels and tobacco also produce anthropogenic releases of cadmium into the environment (HSDB, 1993).

Background Cd levels in soils should not exceed 0.5 ppm, and all higher values reflect anthropogenic impact (Kabata-Pendias and Pendias, 1984).

H.1.3.2 Physical and Chemical Properties of Cadmium

Molecular Weight	112.00[1]
Water Solubility, mg/l	0.0E+00[2]
Vapor Pressure, mm Hg	0.0E+00[3]
Bioaccumulation Factor for Fish	2.0E+02[4]
Bioaccumulation Factor for Shellfish	2.0E+03[4]

Sources: [1]Multi-Media Exposure Assessment Manual, 1989
[2]Weast, 1979
[3]USEPA, 1981
[4]Napier, 1980

H.1.3.3 Environmental Fate and Transport

In a U.S. air sampling study, most ambient air levels of cadmium were <10 ng/m^3, which is very near the detection limit (Carson et al., 1987). Cadmium can enter surface water due to a variety of manufacturing operations, such as electroplating and discarding of spent electroplating solutions (HSDB, 1993).

Several studies have concluded that adsorption, rather than precipitation, control CD concentrations in soil solutions until a threshold pH value (i.e., pH 7.5) is exceeded. Cd is most mobile in acidic soils within the range of pH 4.5 to 5.5, whereas in alkaline soils, Cd is rather immobile (Kabata-Pendias and Pendias, 1984).

H.1.3.4 Routes of Exposure, Distribution, Absorption, Transport, and Degradation

Cd is an airborne workplace contaminant, but exposure is of greater concern to the general population. It is found in food stuffs such as grains, meat, fish and fruit, in contaminated air, water, and soil, as well as in cigarette smoke. Humans are exposed to cadmium via inhalation and ingestion, at which time the metal can be transported through the bloodstream to vital organs (Clayton and Clayton, 1981). In the blood, a small molecular weight plasma protein known as metallothionien binds cadmium. The elimination half-life of cadmium is long (16-33 yrs), but decreases under conditions of acute exposures.

Gastrointestinal absorption of cadmium in humans ranges from 5-6% (USEPA, 1985a) Pulmonary absorption of cadmium in humans is reported to range from 10% to 50% (CDHS, 1986). Cadmium bioaccumulates in humans, particularly in the kidney and liver (USEPA, 1985a,b).

H.1.3.5 Acute Toxicity

Acute toxic effects associated with cadmium compounds can occur in humans under unusually intense exposure scenarios, such as intentional or accidental poisoning. Symptoms of acute non-fatal toxicity resulting from consumption of drinks contaminated with an estimated 16 mg/l of cadmium included nausea, vomiting, and abdominal pain. Inhalation of cadmium fumes may result in acute chemical pneumonitis and pulmonary edema (ATSDR, 1989).

H.1.3.6 Chronic Toxicity

Chronic oral or inhalation exposure of humans to cadmium has been associated with renal dysfunction, itai-itai disease (bone damage), hypertension, anemia, endocrine alternations, immunosuppression, and irreversible lung damage in the form of chronic bronchitis and emphysema (Clayton and Clayton, 1981).

Progressive accumulation of Cd in soft tissues, particularly the kidney, poses a serious human health risk. A higher incidence of kidney damage reported for certain regions of Japan has been linked to a high intake of dietary cadmium. Renal toxicity occurs in humans at a renal cortex concentration of cadmium of 200 about μg/g (USEPA, 1985b).

H.1.3.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Numerous assays of cadmium's genotoxic potential have been conducted, yielding mixed results. Bacterial gene mutation assays have been conducted using Salmonella strains, and three of four were reported to be negative, although some positive or weak positive responses were indicated in one study. Tests for chromosomal aberrations involving human and other mammalian cells have also yielded mixed results. In vitro tests of human blood lymphocytes were positive in one case, weakly positive in a second case, and negative in two cases. Human W138 and MCR5 cells also yielded negative results. Results were positive using chinese hamster cells, but negative using mouse mammary carcinoma cells (ATSDR, 1989).

Carcinogenicity

Epidemiological studies have demonstrated a strong association between inhalation exposure to cadmium and cancers of the lungs, kidneys, and prostate (USEPA, 1985b). In experimental animals, cadmium induces injection-site sarcomas and testicular tumors. When administrated by inhalation, cadmium chloride is a potent pulmonary carcinogen in rats. Cadmium is a well-documented animal teratogen (USEPA, 1985b). Several animal studies support this data. Chronic inhalation exposure of rats to cadmium produce lung tumors in Wistar rats, and tumors at various sites (including mammary tumors in females) in Fischer rats (IRIS, 1994).

Teratogenicity

Teratogenic effects of cadmium administered at high doses in bioassays is abundantly documented, but little evidence directly addresses the question of whether lower, environmentally realistic doses might exert such effects (ATSDR, 1989).

H.1.3.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

Cadmium is classified as a probable human carcinogen (Class B1). This classification applies to agents for which there is limited evidence of carcinogenicity in humans from epidemiologic studies but significant evidence in animals.

This designation is based on a higher incidence of lung cancer in cadmium smelter workers, and increased incidence of prostrate cancer in battery workers.

EPA Dose-Response Parameters (IRIS, 1994)

Carcinogenic effects:

Limited evidence from occupational epidemiologic studies of cadmium exposure is consistent across investigators and study populations. There is sufficient evidence of carcinogenicity in rats and mice by inhalation and intramuscular and subcutaneous injection. Seven studies in rats and mice where in cadmium salts (acetate, sulfate, chloride) were administered orally have shown no evidence of carcinogenic response.

There is no oral Cancer Slope Factor for cadmium.

INHALATION UNIT RISK: 1.8E-3 per (µg/cu.m)

Noncarcinogenic Effects:

ORAL RfD and SUMMARY:

5E-4 mg/kg/day (water)

1E-3 mg/kg/day (food)

CRITICAL EFFECT/TARGET ORGAN: significant proteinuria in human subjects

ORAL RfD UNCERTAINTY :

UF = 10. This uncertainty factor is used to account for intrahuman variability to the toxicity of this chemical in the absence of specific data on sensitive individuals.

ORAL RfD MODIFYING FACTOR :

MF = 1.

ORAL RfD CONFIDENCE :

Study: Not applicable

Data Base: High

RfD: High

INHALATION RfD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

H.1.3.9 References

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H.1.4 Chloroform

H.1.4.1 Background

Chloroform ($CHCl_3$) is a volatile and relatively soluble liquid (in water and fat) that is used principally as an industrial solvent and as a chemical intermediate (Fawell and Hunt, 1988). Chloroform at trace levels is ubiquitous in the environment with average urban ambient atmospheric concentrations less than 1000 ppt (parts per trillion) and rural air concentrations less than 10 ppt (U.S. Environmental Protection Agency, 1985). A drinking water survey in the United States indicated a range of concentrations from 0.1 to 311 mg/liter with a median concentration of 21 mg/liter (WHO, 1984). Inhalation is believed to be the primary route of exposure under normal circumstances, followed by ingestion of chloroform contaminated drinking water (U.S. Environmental Protection Agency, 1985). Respiratory absorption efficiency ranges from 49 to 77 percent (U.S. Environmental Protection Agency, 1980), which is influenced by body weight, fat content, and solubility of chloroform in blood (U.S. Environmental Protection Agency, 1985). Absorption of chloroform from the gastrointestinal tract in humans is complete (Fry and others, 1972). Once absorbed, chloroform is readily distributed to all tissues, especially those with a high lipid content. Tissues with the highest chloroform concentrations (in descending order) are adipose tissue, brain, liver, kidney, and blood (McConnell and others, 1975).

H.1.4.2 Acute Toxicity

In humans and experimental animals, the principal effects of acute chloroform exposure are central nervous system (CNS) depression, hepatotoxicity (liver toxicity), and to a lesser extent, kidney and cardiac effects (U.S. Environmental Protection Agency, 1985). Chloroform is of low acute toxicity with an oral LD_{50} in male and female rats of 908 mg/kg and 1117 mg/kg, respectively (Chu and others, 1980).

The depressive effect of chloroform on the CNS is focused on the cortex, higher brain centers, medulla and spinal cord (Wood-Smith and Stewart, 1964). Brain centers responsible for respiration, vomiting, temperature regulation, vasomotor and vagal activity are all depressed (Adriani, 1970; U.S. Environmental Protection Agency, 1985). Hepatotoxicity is characterized

by rapid glycogen depletion, fatty degeneration and centrilobular necrosis (tissue destruction) with corresponding symptoms of progressive weakness, prolonged vomiting, coma and even death, usually by the fourth or fifth day in severe cases (U.S. Environmental Protection Agency, 1985). Clinical evidence of altered liver function include increased serum bilirubin, bile in urine, increased nitrogen excretion and reduced creatine clearance (U.S. Environmental Protection Agency, 1985).

Other organs adversely affected by acute exposures to chloroform include the respiratory tract (increased respiratory rate), cardiovascular system (arrhythmias and reduced blood pressure), urinary tract (decreased urine flow), and hematologic effects (increased number of red blood cells, leukocytes, and polymorphonuclear cells) (U.S. Environmental Protection Agency, 1985). The systemic effects of chloroform are independent of route of exposure.

H.1.4.3 Chronic Toxicity

Most of the data on the chronic toxicity of chloroform has been obtained from carcinogenicity studies. In humans the most common toxic effects of chronic chloroform exposure is on the liver and CNS. Liver effects have been observed for experimental animals and occupationally exposed human populations. Symptoms observed in workers exposed to chloroform (77 to 237 ppm) include thirst, irritability, lassitude, mental sluggishness, and loss of appetite (NIOSH, 1974; Challen and others, 1958). Also, no liver damage was observed. Several researchers observed jaundice, enlarged livers, and increased incidence of viral hepatitis in occupationally exposed workers (Bomski and others, 1967; Phoon and others, 1983). Daily consumption of chloroform by humans in toothpaste and mouthwash was studied over a five-year period (WHO, 1984). No liver toxicity was observed at daily consumption rates estimated at 0.34 - 0.96 mg/kg (WHO, 1984). Chronic animal exposure studies have also indicated kidney damage and CNS depression in chloroform treated animals (ATSDR, 1987).

Carcinogenicity

There are no epidemiological studies on the carcinogenicity of chloroform. There are several epidemiological studies of the effects of chlorinated drinking water studies which indicate a small

significant increase in the incidence of bladder or colon cancer (U.S. Environmental Protection Agency, 1990). These studies are not conclusive since many other carcinogenic compounds were also present.

There is sufficient evidence of animal carcinogenicity of chloroform, specifically in the kidneys and livers of exposed rats and mice (ATSDR, 1987). In a drinking water study designed to examine the carcinogenicity of chloroform at low doses, rats and mice received up to 160 mg/kg/day and 263 mg/kg/day, respectively for 104 weeks (Jorgenson and others, 1985). A significant and dose-related increase in the incidence of renal (kidney) tumors was observed (U.S. Environmental Protection Agency, 1990). In another carcinogenic study, rats and mice were fed chloroform at varying doses for 78 weeks (NCI, 1976). Upon examination, a significant increase in kidney epithelial tumors in male rats and hepatocellular (liver) carcinomas in mice was observed (NCI, 1976). The USEPA has reviewed the available data on carcinogenicity and has categorized chloroform as a probable human carcinogen (Group B_2) based on an increased incidence of several tumor types in rats and three strains of mice (U.S. Environmental Protection Agency, 1990).

Mutagenicity

Most mutagenic tests have produced negative in vitro and in vivo results for chloroform. Specifically, negative results have been obtained in tests examining covalent binding to DNA, Ames Salmonella histidine reversion, DNA damage, and chromosomal aberrations (U.S. Environmental Protection Agency, 1990). In contrast, chloroform caused mitotic recombination in bacteria and sister chromatid exchange in human lymphocytes and mouse bone marrow cells after in vivo exposure (U.S. Environmental Protection Agency, 1990). The carcinogenicity of chloroform may be the result of metabolism to phosgene, which is known to cause DNA cross-links (U.S. Environmental Protection Agency, 1990). As supporting evidence of this theory, urine extracts from chloroform-treated mice were found to be mutagenic (Agustin and Lim-Syliance, 1978).

Reproductive/Developmental

There is very little data on the reproductive effects of chloroform in animals and no human data are available. Inhalation of chloroform (400 to 800 ppm), for 4 hrs/day for 5 days resulted in an increase in the rate of abnormal sperm in exposed mice (Land and others, 1981). This effect was not seen following intraperitoneal injection. Additionally, gonadal atrophy was seen in rats orally treated with chloroform for 13 weeks up to 410 mg/kg/day (Palmer and others, 1979).

No data was available on the developmental effects of chloroform in humans. Chloroform was shown to readily cross the placenta and accumulate in the amniotic fluid (Danielsson and others, 1986). Associated developmental effects of high doses of chloroform in animals include fetal resorptions, decreased fetal weight, increased incidence of cleft palate and incomplete development of skull bones (ATSDR, 1987).

Sensitive Populations

The laboratory studies showed a distinctive strain difference in toxic effects to the kidney (for example, strains that more effectively metabolize chloroform to phosgene are more sensitive) (ATSDR, 1987). Also, a sex related difference in susceptibility to kidney effects was observed where male mice are much more sensitive to chloroform than are females. This differential sensitivity is thought to be linked to higher testosterone levels in males. Human males may also have an increased chloroform sensitivity. Dietary factors (in other words, ethanol exposure and starvation) are known to potentiate the effects of chloroform.

Chemical Interactions

Chloroform toxicity is affected by any factor which alters its metabolism (U.S. Environmental Protection Agency, 1985). Metabolism of chloroform to more reactive compounds is well documented; therefore co-exposure to compounds that enhance metabolism would increase the toxicity of chloroform (ATSDR, 1987).

Many compounds are known to induce liver microsomal enzyme activity and thereby potentially enhance chloroform toxicity, such as ethanol, polybrominated biphenyls, polychlorinated

biphenyls, and ketones such as chlordecone (ATSDR, 1987; U.S. Environmental Protection Agency, 1985). In contrast, disulfiram, diethyldithiocarbamate and carbon disulfide inhibit metabolizing enzymes and protect against chloroform hepatotoxicity (ATSDR, 1987).

Dose-Response Parameter Estimates

The dose-response parameter estimates for carcinogens and noncarcinogens are computed differently by the USEPA; therefore, these estimates are presented separately below.

Carcinogenic Effects:

Chloroform is classified as a probable human carcinogen (Group B2) by the USEPA. The Cancer Assessment Group (CAG) of USEPA has computed an oral cancer potency estimate of 6.1×10^{-3} $(mg/kg/day)^{-1}$ (U.S. Environmental Protection Agency, 1990). This estimate was based on several studies involving rats and mice which experienced increased incidences of hepatocellular carcinomas, and renal and liver tumors (NCI, 1976; Jorgenson and others, 1985). An inhalation cancer potency factor of 8.1×10^{-3} $(mg/kg/day)^{-1}$ was derived by the USEPA using a root-to-root extrapolation of the oral cancer potency factor as stated above (U.S. Environmental Protection Agency, 1990).

Oral Cancer Potency Estimate: 6.1×10^{-3} $(mg/kg/day)^{-1}$ (U.S. Environmental Protection Agency, 1990).

Inhalation Cancer Potency Estimate: 8.1×10^{-2} $(mg/Kg/day)^{-1}$ (U.S. Environmental Protection Agency 1990).

Noncarcinogenic Effects:

The Office of Health and Environmental Assessment has derived a chronic oral reference dose of 1×10^{-2} mg/kg/day (U.S. Environmental Protection Agency, 1990) based on an increased levels of SGPT and SGOT in high-dose animals (beagle dogs administered doses of 30 mg/kg/day for 6 days/week for 7.5 years) (Heywood and others, 1979). Uncertainty factors of '0 each were applied to the LOAEL of 12.9 mg/kg/day to account for the interspecies

conversion, protection of sensitive human subpopulations, and concern that the effects seen was a LOAEL and not a NOAEL (U.S. Environmental Protection Agency, 1990). An inhalation RfD is not currently available.

Oral RfD: 1×10^{-2} mg/kg/day (U.S. Environmental Protection Agency, 1990).

H.1.4.4 References

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H.1.5 Chromium

H.1.5.1 Occurrence and Use

Chromium is a naturally occurring element that is found in soil and in volcanic dust and gases. It is found in the environment in three major states: chromium (0), chromium (III), and chromium (VI). It is only found in nature as in combined oxidation states, and not in the zero valence state (IARC 1980). This profile focuses on the two most common forms of the metal, chromium (III) and chromium (IV).

Chromium (III) occurs naturally in the environment. With the exception of acetate and nitrate salts, the trivalent chromium compounds are generally insoluble in water. In most biological systems, chromium is present in the trivalent form. It is an essential nutrient required in trace quantities for normal glucose metabolism (Anderson 1981).

Chromium (VI) rarely occurs in nature apart from anthropogenic sources because it is readily reduced in the presence of oxidizable organic matter. With the exception of a few compounds, hexavalent chromium exists only as oxo species that are strong oxidizing agents. The oxidizing potential of chromate ions depends on pH. Chromate and dichromate compounds are the most common forms of hexavalent chrome. They are soluble and stable in natural waters because of the low concentration of reducing matter (EPA 1984). The ammonium and alkali metal salts of hexavalent chromium are also generally water soluble, whereas the alkaline metal salts (eg. calcium, strontium) are less soluble in water.

Chromium (VI) and Chromium (0) are produced by industrial processes. The metal Chromium (0) is a steel-gray solid with a high melting point. Chromium is used mainly for making steel and other alloys. In the form of the mineral chromite, it is used by the refractory industry to make bricks for metallurgical furnaces. Chromium compounds produced by the chemical industry are used for chrome plating, the manufacture of pigments, leather tanning, wood treatment, and water treatment (ATSDR, 1989).

H.1.5.2 Physical and Chemical Properties of Chromium III and Chromium VI

Molecular Weight	52.00[1]
Water Solubility, mg/l	0.0E+00[2]
Vapor Pressure, mm Hg	0.0E+00[3]
Bioaccumulation Factor for Fish	2.0E+01[4]
Bioaccumulation Factor for Shellfish	2.0E+03[4]

Sources: [1]Multi-Media Exposure Assessment Manual, 1989
[2]Weast, 1979
[3]USEPA, 1981
[4]Napier et al., 1980

H.1.5.3 Environmental Fate and Transport

Chromium occurs naturally in the earth's crust. Soil chromium levels were reported as follows: 37 ppm geometric mean in the USA (Shacklette and Boerngen 1984) and 5-3,000 ppm with 0.5 - 10,000 ppm extreme limits (Dragun 1988). In soil, chromium probably occurs as insoluble Cr (III) oxide (Cr_2O_3-nH_2O), since the organic matter in soil tends primarily to convert soluble chromate (chromium (VI)) to insoluble Cr_2O_3 . Chromium in soil may be transported to the atmosphere in the form of aerosol, while runoff and leaching may transport chromium from soil to surface waters and groundwaters. Flooding of soils and the subsequent anaerobic decomposition of plant matters may increase mobilization of chromium in soils due to formation of soluble complexes with humic substances.

Chromium is primarily removed from the atmosphere by fallout and precipitation. Atmospheric chromium removed by physical processes enters surface water or soil predominantly; however, prior to their removal, chromium particles of aerodynamic diameter (less than 20 um) may remain airborne for long periods and may be transported long distances. In the atmosphere, chromium (VI) may be reduced to chromium (III) at a significant rate by vanadium (V^{2+}, V^{3+} , and VO_2^+), Fe^{2+} , HSO_3^- and AS^{3+} (EPA 1987).

Because there are no known chromium compounds that can volatilize from water, transport of chromium from water to the atmosphere is not likely other than by transport by windblown sea sprays. In surface waters, chromium may be transported in five forms, as follows: 1) in solution and organic complexes, 2) adsorbed 3) precipitated and co-precipitated 4) in organic solids and 5) in sediments (Towill, et al., 1978). The exact chemical forms of chromium in surface waters are not well defined. Although most of the soluble chromium in surface water may be present as Cr (VI) (Towill, et al., 1978), a small amount may be present as Cr (III) organic complexes (DeGroot and Allersma, 1978; Fukai, 1967). Most of the chromium (III) in surface water is eventually expected to precipitate in sediments. Small amounts of chromium (III) may remain in solution as soluble complexes. Chromium (VI) will predominantly be present in soluble form. Chromium (VI) will eventually be reduced to chromium (III) by organic matter present in water. The residence time of chromium in lake water was estimated to be between 4.6 to 18 years.

The oxidation of chromium (III) to chromium (VI) by solid MnO_2 in water remained unaffected by dissolved oxygen, and the process was very slow in slightly acidic (pH 6) and basic solutions (pH 11) because of the low solubility, the $Cr(OH)^3$ that is formed at these pHs (Eary and Rai 1987). Therefore, this oxidation process would not be significant in most natural waters where the pH range is usually between 6 and 9 because this process is very slow in slightly acidic water. Similar oxidation of chromium (III) to chromium (VI) in the atmosphere is unlikely (EPA 1987).

H.1.5.4 Routes of Exposure, Absorption, Distribution, Transport, and Degradation

The general population is exposed to small amounts of chromium results by breathing air, and ingesting drinking water and food containing chromium. Much higher exposure to chromium results from working in certain chromium industries and to people who smoke cigarettes. The two largest sources of chromium emissions in the atmosphere are from the chemical manufacturing industry and the combustion of natural gas, oil, and coal. A detailed list of other sources of exposure to chromium can be found in the ATSDR Toxicologic Profile (1989).

Chromium can enter the body via oral, inhalation and dermal exposure. For the general population, the gastrointestinal tract is the primary route of entry, although entry through the airways can be significant near industrial sources. Following occupational exposure, the airways and skin are the primary routes of uptake. Inhalation studies conducted using animals indicate that 53% to about 85% of the chromium from chromium (VI) compounds is cleared from the lungs after intratracheal injection compared to 5 to 30% clearance of the chromium from chromium (III) compounds (Baetjer, et al., 1959, Visek, et al., 1953, Wiegand, et al., 1984).

Via the oral route, Donaldson and Barreras (1966) found that about 0.4% of the radioactive chromium from an oral dose of a labelled compound containing chromium (III) was absorbed and about 10.6% of the labelled compound containing chromium (VI) were absorbed in humans. Anderson, et al., (1983) confirmed minimal (about 0.4%) gastrointestinal absorption of dietary and supplemental chromium in humans. The supplemental chromium was provided as a tablet containing 200 μg chromium (III) as chromic chloride.

In the dermal studies, using volunteers, Mali (1963) found that potassium dichromate (VI) but not chromic (III) sulfate penetrated intact epidermis. Samitz and Shrager (1966) found that absorption of chromic sulfate was negligible, with slightly larger amounts of chromium (III) nitrate absorbed. The absorption of chromic (III) chloride was similar to potassium dichromate. Randall and Gibson (1987), and Lindberg and Vesterberg (1983), indicate some absorption of chromium (III) and (VI) via the skin.

Following inhalation exposure to chromite (III) dust for 28 days, chromium is absorbed and distributed in animals to the kidneys, lungs and spleen (Kamiya, et al., 1981). Once absorbed, chromium (VI) is reduced to chromium (III) (Kitagawa, et al., 1982, Levis, et al., 1978). During reduction of chromium (VI) in the plasma, chromium protein complexes are formed; these complexes are excreted by the kidneys. Formation of these complexes can be harmful if they occur at high enough levels. In addition, chromium (VI) crosses cell membranes easily and is reduced inside cells, forming chromium protein complexes during reduction. Once complexed with protein, chromium cannot leave the cell. Chromium (III) crosses cell membranes less

readily, does not readily bind to intracellular protein and can diffuse out. Chromium (VI) can be reduced to chromium (III) in vitro by gastric juice, but whether intragastric reduction occurs in vivo is not known.

The toxicity of chromium is attributed primarily to the hexavalent form. In humans and experimental animals, gastrointestinal absorption of inorganic salts of chromium III is low (from 0.5% to 3%). However, organic complexes of chromium III are more readily absorbed (approximately 10% to 25%). The spleen and kidneys of rats were shown to have the highest concentration of chromium when chromium chloride intravenous doses (Hopkins, 1965) or chromic chloride in drinking water (Mackenzie et al., 1958) were administered. (EPA, 1985; Casarett and Doull, 1986).

H.1.5.5 Acute Toxicity

A wide variety of acute effects have been observed in humans, including contact dermatitis, skin ulcerations, kidney failure, nasal irritation, nosebleeds, respiratory congestion, teeth erosion and discoloration, stomachaches and kidney failure. These effects are reported to be much more severe for Chromium VI exposure than for Chromium III exposure.

Langard and Norseth (1986) indicated that oral doses of 2-5 g of unspecified chromate compounds (chromium (VI)) are fatal to humans. Acute poisoning symptoms included gastrointestinal bleeding, massive fluid loss and death in some individuals following cardiovascular shock. These effects tended to occur within 12 hr of ingestion. When the ingested dose was reduced to less than, or equal to, 2 g, tubular renal necrosis and diffuse liver necrosis developed and contributed to the cause of death in fatal cases. Liver and kidney effects developed 1 to 4 days after ingestion.

Via the dermal route, patients died after antiscabies ointment containing chromium (VI) was applied to the skin (Brieger 1920). Symptoms included necrosis at the application site, nausea, vomiting, shock and coma. Autopsies revealed tubular necrosis and hyperemia of the kidney. Other reviews of death after dermal exposure to chromium compounds include Major (1922) and

Fritz, et al., (1959). It is important to note that these cases involved damaged rather than intact skin.

H.1.5.6 Chronic Toxicity

Long-term oral exposure of animals to relatively low levels of chromium compounds has not resulted in systemic toxic effects. The effects of chromium (VI) on the nasal mucosa and lung function in humans may be the most sensitive noncancer end point for chronic inhalation exposure to chromium (VI) compounds. Other effects observed following chromium (VI) exposure include effects on the immune system, nervous system and liver. Dermal exposure to both chromium (III) and chromium (VI) can result in chromium sensitization.

In a Russian study (Kuperman 1964), 10 normal individuals were exposed to chromium (VI) aerosols of unspecified composition at 0.0015 to 0.04 mg/m^3. Concentrations of 0.01-0.024 mg/m^3 chromium (VI) sharply irritated the nose when inhaled for short periods. The most sensitive individual responded at a concentration of 0.0025 to 0.004 mg/m^3 chromium (VI). It was not known if this was a reaction to chromium (VI) or to the acidity of the aerosol. Many cases of nasal mucosal injury (inflamed mucosa, ulcerated or perforated septum) in workers exposed to CrO_3 have been reported (Bloomfield and Blum 1928, Gresh 1944, Zvaifler 1944, Klienfeld and Russo 1965, Vigliani and Zurlo 1955). Effects occurred at chromium (VI) concentrations ranging from 0.06 to 0.72 mg/m^3. The length of exposure to these cases was highly variable. Cohen and Kramkowski (1973) and Cohen, et al., (1974) found that 12/37 workers employed by a chrome-plating plant developed nasal ulceration or perforation within 1 year of being employed. Airborne chromium (VI) concentrations ranged from less than 0.71 to 9.12 $\mu g/m^3$. Other reported cases of nasal and lung effects due to chromium exposure are (Hanslian, et al., 1967, Markel and Lucas 1973 and Lindberg and Hedenstierna 1983).

Other respiratory effects have been reported in workers exposed to chromium compounds. Alwens and Jonas (1938), Fischer-Wasels (1938), Koelsch (1938), Lehmann (1932), Mancuso (1951) reported that workers exposed chronically to chromate (VI) dust resulted in chronic irritation of the respiratory tract, congestion and hyperemia, chronic rhinitis, congestion of the larynx, polyps

of the upper respiratory tract, chronic inflammation of the lungs, emphysema, tracheitis, chronic bronchitis, chronic pharyngitis, and perivascular lung markings, enlargement of hilar region lymph nodes and adhesions of the diaphragm.

Although immune effects have not been reported in humans following exposure to chromium compounds, immune effects have been reported in animals. Inhalation exposure to chromium (VI) and chromium (III) compounds at concentrations of 0.2 - 0.9 mg/m^3 resulted in depression of some indices of immune system function in animals, whereas chromium (VI) at concentrations of less than 0.1 mg/m^3 chromium resulted in stimulation. For a review, see Steven, et al., (1976), Camner, et al., (1974) and Waters, et al., (1975).

Sensitization can occur after exposure of humans and guinea pigs to chromium via the dermal route (Maloof 1955, Milner 1980, Avnstorp and Menne 1982, Husain 1977, Gross, et al., 1968, Schwartz-Speck and Grundsman 1972, Jansen and Berrens 1968, Siegenthaler, et al., 1983). Although reactions to chromium (VI) are more common, reactions to chromium (III) can also occur. Inhalation exposure of workers to chromium compounds may also result in sensitization (Moller, et al., 1986). Because the development of hypersensitivity is highly variable between individuals, it is not possible to develop a generalizable dose-response relationship for this effect.

Chromium may have central nervous system effects (Diaz-Mayans, et al., 1986 and Mathur, et al., 1977). Mathur, et al., 1977 reported changes in brains of rabbits given daily intraperitoneal doses of chromium (III) nitrate or potassium dichromate (VI) at 2 mg/kg chromium for 3 or 6 weeks. These changes included neuronal degeneration in the cerebral cortex, marked chromatolysis, nuclear changes in neurons, neuronal degeneration in the cerebral cortex accompanied by neuronophagia, neuroglial proliferation and meningeal congestion. Abnormal deposits of chromium in the brains of patients with encephalopathies treated with radiological contrast substances containing chromium (Dockett 1986) provide limited evidence that the brain may also be a target organ for chromium toxicity in humans.

Chromium is a nephrotoxin producing tubular necrosis, with low doses acting specifically at the proximal convoluted tubule of the kidney. Human and animal studies do not clearly define the doses that produce adverse effects. Powers, et al., (1986) reported marked acute proteinuria, glycosuria, phosphaturia, enzymuria, severe electrolytic imbalance, increased kidney weight and morphological changes in the kidneys of rats given a single subcutaneous injection of sodium dichromate (chromium (VI)) at a dose of 20 mg/kg. Animal studies documenting kidney effects include Kirschbaum, et al., 1981, Baines 1965, Evan and Dail 1974, Powers, et al., 1986, Laborda, et al., 1986, Berndt 1976 and Srivastava, et al., 1985.

Liver effects have occurred in humans and animals following inhalation and parenteral exposure to chromium compounds. Hepatic changes observed in animals exposed daily for 3-6 weeks to chromic compounds (2 mg/kg of chromic (III) nitrate or potassium dichromate (VI)) included congestion and dilation of the central veins and sinusoids, discrete foci of necrosis and hemorrhage in liver parenchyma, nuclear pleomorphism, multinucleated cells in the lobules and bile duct proliferation. Studies indicate chromium (VI) caused more damage than chromium (III).

H.1.5.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Results of in vivo mutagenicity studies have consistently shown positive results for chromium (VI) compounds (Rasmuson 1985, Knudsen 1980, Paschin, et al., 1982, Newton and Lilly 1986, Bigaliev, et al., 1978, Wild 1978, DiPaolo and Castro 1979, Bigaliev, et al., 1977 and Sarto, et al., 1982) and negative results for chromium (III) compounds (Wild 1978) in standard tests. Other in vitro studies reviewing mutagenicity of chromium include Bianchi and Levis 1985, EPA 1984, Bonati, et al., 1976 and Singh 1983. These results support the carcinogenicity findings in animal studies for chromium. Chromium (III) has tested positive in only isolated nuclei and purified DNA, in studies at high concentrations and in cells with phagocytic activity. The difference in activity of the two valence states of chromium is a result of differences in ability to permeate cell membranes.

Carcinogenicity

Epidemiological studies reviewed in IARC (1980, 1982, 1987) and EPA (1984) clearly indicate an increased respiratory cancer risk in chromate production workers (Baetjer 1950, Alderson, et al., 1981, Hayes, et al., 1979, Machle and Gregorius 1948, Mancuso and Heuper 1951, Mancuso 1975, Ohsaki, et al., 1978 and Taylor 1966). Increased risks of respiratory cancer have also been found in some studies of chrome pigment workers (Langard and Norseth 1975 and Davies 1984), chrome-plating workers (Franchini, et al., 1983, Sorahan, et al., 1987) and ferrochromium workers (Langard, et al., 1980). Mancuso (1975) found that the lung cancer mortality was dose-related to total chromium exposure and with a latency period of 27-36 years after initial exposures. The epidemiological studies do not clearly implicate specific compounds, but do implicate chromium (VI), as opposed to Cr (III), as the carcinogenic form. Based on the epidemiological evidence, the EPA (1987) and IARC (1987) have concluded that exposure to chromium (VI) compounds via the inhalation route is carcinogenic to humans.

Teratogenicity

There are no human or animal studies of developmental toxicity following inhalation, oral or dermal exposure to chromium. Exposure to chromium (III) or chromium (VI) compounds may result in developmental effects via the parenteral route, however. In studies by Gale (1978) and Gale and Bunch (1979), increased fetal death and an increase in external abnormalities were observed in hamsters treated by intravenous injection with CrO_3 (chromium (VI)) on a single day of gestation. Matsumoto, et al., 1976 observed fetal weight depression and an increase in external abnormalities in the fetuses of mice treated intraperitoneally with $CrCl_3$ at 14.64-24.4 mg/kg chromium (III) on the eighth day of gestation. No effects were observed at 9.76 mg/kg.

Some studies indicate that chromium (III) and chromium (VI) compounds may affect reproduction. Behari, et al., 1978 observed testicular effects in rabbits injected intraperitoneally with chromium (III) nitrate or potassium dichromate (VI) at 2 mg/kg/day for 3 or 6 weeks. Microscopic examination of the testes showed thickening of the tunica albuginea, congestion of blood vessels and degenerative changes of the seminiferous epithelium in chromium (III)-treated

rats. Chromium (VI) treatment resulted in mild edema of the interstitial tissue and congestion of the blood vessels; at 6 weeks the tubules were devoid of spermatocytes.

H.1.5.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

EPA (1994) has classified inhaled chromium VI in Group A - Human Carcinogen by inhalation. Chromium (III) is not considered to be a carcinogen.

Carcinogenic Effects of Chromium III:

The EPA (1994) has not evaluated chromium (III) for human carcinogenic potential.

Carcinogenic Effects of Chromium VI:

INHALATION UNIT RISK: 1.2E-2 per (μg/cu.m) or

$4.1 \times 10^{+1}$ $(mg/kg/day)^{-1}$

DISCUSSION OF CONFIDENCE :

The inhalation cancer potency factor was derived from a study based on the occupational exposure of workers to chromium and deaths from lung cancer (Mancuso 1975). Results of studies of chromium exposure are consistent across investigators and countries. A dose-relationship for lung tumors has been established. The assumption that the ratio of Cr III to Cr VI is 6:1 may lead to a 7-fold underestimation of risk. The use of 1949 hygiene data, which may underestimate worker exposure, may result in an overestimation of risk. Further overestimation of risk may be due to the implicit assumption that the smoking habits of chromate workers were similar to those of the general white male population, since it is generally accepted that the proportion of smokers is higher for industrial workers than for the general population.

Because there is no evidence for the carcinogenicity of chromium compounds by the oral route of administration, the EPA has not derived an oral cancer potency factor (EPA 1994, 1993) for chromium (VI).

Noncarcinogenic Effects of Chromium III:

ORAL RfD: 1E+0 mg/kg/day (as an insoluble salt)

CRITICAL EFFECT/TARGET ORGAN: No effects observed

ORAL RfD UNCERTAINTY :

UF = 100. The factor of 100 represents two 10-fold decreases in mg/kg bw/day dose that account for both the expected interhuman and interspecies variability to the toxicity of the chemical in lieu of specific data.

ORAL RfD MODIFYING FACTOR :

MF = 10. The additional modifying factor of 10 is adopted to reflect uncertainty in the NOEL because: 1) the effects observed in the 90-day study were not explicitly addressed in the 2-year study and, thus, the highest NOAEL in the 2-year study may be a LOAEL; 2) the absorption of chromium is low (<1%) and is influenced by a number of factors; thus, a considerable potential variation in absorption exists; and 3) animals were allowed to die naturally after feeding stopped (2 years) and only then was histology performed.

ORAL RfD CONFIDENCE :

Study: Low

Data Base: Low

RfD: Low

The principal study is rated low because of the lack of explicit detail on study protocol and results. Low confidence in the data base reflects the lack of high-dose supporting data. The low confidence in the RfD reflects the foregoing, but also reflects the lack of an observed effect level. Thus, the RfD, as given, should be considered conservative, since the MF addresses only those factors which might lower the RfD.

Noncarcinogenic Effects of Chromium VI:

ORAL RfD: 5E-3 mg/kg/day

CRITICAL EFFECT/TARGET ORGAN: No effects reported

ORAL RfD UNCERTAINTY : UF = 500. The uncertainty factor of 500 represents two 10-fold decreases in dose to account for both the expected interhuman and interspecies variability in the toxicity of the chemical in lieu of specific data, and an additional factor of 5 to compensate for the less-than-lifetime exposure duration of the principal study.

ORAL RfD CONFIDENCE :

Study: Low

Data Base: Low

Confidence in the chosen study is low because of the small number of animals tested, the small number of parameters measured and the lack of toxic effect at the highest dose tested. Confidence in the data base is low because the supporting studies are of equally low quality, and teratogenic and reproductive endpoints are not well studied. Low confidence in the RfD follows.

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H.1.6 Copper

H.1.6.1 Occurrence and Use

Copper is ubiquitous in the earth's crust, primarily found as sulfides and oxides. Natural levels in soil range from 8 to 90 mg/kg (Kabata-Pendias and Pendias, 1984).

About half of copper production is used as a conductor in electrical equipment due to its high conductivity. It is used in many alloys: beryllium-copper, brass, bronze, gunmetal, bell metal, german silver, etc. These are used in plumbing, electronics, and the manufacture of various parts and goods. Copper compounds are used in pesticides, antifouling paints, algicides, fungicides, and insecticides. Some compounds are used as pigments in paints and ceramics (Carson et al., 1987).

H.1.6.2 Physical and Chemical Properties of Copper

Molecular Weight	63.55[1]
Water Solubility, mg/l	0.0E+00[2]
Vapor Pressure, mm Hg	0.0E+00[3]
Bioaccumulation Factor for Fish	5.0E+01[4]
Bioaccumulation Factor for Shellfish	4.0E+02[4]

Sources: [1]Multi-Media Exposure Assessment Manual, 1989
[2]Weast, 1979
[3]Lyman et al., 1982
[4]Napier et al., 1980

H.1.6.3 Environmental Fate and Transport

Factors affecting deposition of copper in soil include the degree of weathering, the nature and intensity of the soil formation, drainage, pH, oxidation-reduction potential, and the amount of organic matter in the soil. Since copper is likely to be more mobile under acidic than alkaline conditions, the relation of pH to copper in the environment has been of great concern to agriculturalists and biologists. Alkaline conditions in the soil and surface water favor

precipitation of copper. Acid conditions promote solubility of copper, increase the concentration ionic copper, and thereby change the microorganism and other aquatic animal populations, depending on tolerance for various levels of copper in solution. In soils exposed to atmospheric deposition, high levels of copper and other metals may occur that can be directly toxic to certain soil microorganisms and can disrupt important microbial processes in soil, such a nutrient cycling (HSDB, 1992).

H.1.6.4 Routes of Exposure, Distribution, Absorption, Transport, and Degradation

The principal route of exposure to copper is by ingestion of contaminated food and water, although inhalation exposure can occur in the workplace. Copper is absorbed in the stomach and duodenum, and typically about half of a dose will be absorbed. The main sites of deposition are the liver brain and muscles, and a 70-kg adult stores 70 to 120 mg. The major excretion route is the bile (Carson et al., 1987). Copper is an essential nutrient, but is toxic to humans at high levels.

H.1.6.5 Acute Toxicity

Exposure to metallic copper dust by inhalation can cause a short-term illness similar to metal fume fever that is characterized by chills, fever, aching muscles, dryness of the mouth and throat, and headache. Exposure to copper fumes can produce upper respiratory tract irritation, a metallic or sweet taste, nausea, and occasional discoloration of skin and hair. Individuals exposed to dusts and mists of copper salts may exhibit congestion of nasal mucous membranes, sometimes congestion of the pharynx, and occasionally ulceration with perforation of the nasal septum. If sufficient concentrations of copper salts reach the gastrointestinal tract, they act as irritants and can produce salivation, nausea, vomiting, gastritis and diarrhea. The elimination of ingested ionic copper by vomiting and diarrhea generally protects the patient from more serious systemic toxic effects, which can include hemolysis, hepatic necrosis, gastrointestinal bleeding, oliguria, azotemia, hemoglobinuria, hematuria, proteinuria, hypotension, tachycardia, convulsions and death. Copper salts act as skin irritants upon dermal exposure, producing an itching eczema. Conjunctivitis or even ulceration and turbidity of the cornea may result from the direct contact of ionic copper with the eye (Clement Associates, 1985).

H.1.6.6 Chronic Toxicity

Chronic exposure via inhalation may produce "metal fume fever," which is an influenza-like syndrome, with attacks lasting a day or so. Long-term exposure may also produce nasal ulcerations and bleeding. Anemia has also been observed as a symptom of exposure among workers exposed to copper in the air at levels at of below the TLV (Carson et al., 1987). Chronic exposure of rats and swine via ingestion of copper or its compounds at 2-40 mg/kg/day has resulted in pathological changes of the liver, kidneys, blood, gastrointestinal tract, and in a variety of tissues (ATSDR, 1989).

H.1.6.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Copper appears to increase the mutagenic activity of triose reductase and ascorbic acid in bacterial test systems. However, copper itself does not appear to have mutagenic or teratogenic effects in animals or humans (Clement Associates, 1985).

Carcinogenicity

Available data relating to copper carcinogenicity are presently inadequate. Thus, according to the guidelines of the U.S. EPA, copper is not classifiable as to human carcinogenicity. A long term study of copper hydroxyquinoline administered to mice in their diet yielded negative results in both strains used ($B6C3F_1$ and $B5AKF_1$). However, subcutaneous exposure of male $B6C3F_1$ mice yielded a highly significant elevation in the incidence of reticulum cell sarcomas, although elevated incidences of tumors were not observed in treated $B5AKF_1$ mice or treated female mice of either strain. Studies involving Wistar rats are also presently inconclusive (ATSDR, 1989).

Teratogenicity

Numerous studies have documented the teratogenicity of copper compounds. Bioassay animals to which copper compounds have been shown to be teratogenic include C57BL and DBA strain mice (copper sulfate at 25.9 and 51.7 mg/kg/day), and hamsters (copper sulfate at 2.13 mg/kg and copper citrate a 0.25-1.5 mg/kg)(ATSDR, 1989).

H.1.6.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

Copper is not classified as a human carcinogen (Group D), based on inadequate animal data from assays of copper compounds, equivocal mutagenicity data and lack of any human data.

EPA Dose-Response Parameters (IRIS, 1994)

No carcinogenic or noncarcinogenic dose-response parameters are reported in IRIS for copper. HEAST reports a current drinking water standard of 1.3 mg/l. This can be used to obtain an RfD of 0.0371 mg/kg/day, assuming a 70 kg body weight and water consumption of 2 L/day.

H.1.6.9 References

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H.1.7 Bromodichloromethane

H.1.7.1 Occurrence and Use

Bromodichloromethane is used as a fire retardant, a solvent, as an intermediate for the synthesis of other compounds, and as a heavy liquid for mineral and salt separations (HSDB, 1993).

H.1.7.2 Physical and Chemical Properties of Bromodichloromethane

Molecular Weight	163.80[1]
Water Solubility, mg/l	5.0E+01[2]
Vapor Pressure, mm Hg	5.9E+01[1]
Henry's Law Constant, atm-m^3/mole	3.2E-01[3]
Octanol-Water Partition Coefficient	1.7E+02[1]
Organic Carbon Partition Coefficient	1.1E+02[1]
Bioaccumulation Factor for Fish	3.0E+01[1]
Bioaccumulation Factor for Shellfish	4.9E+00[1]

Sources: [1]Multi-Media Exposure Assessment Manual, 1989
[2]USEPA, 1980
[3]ICF, 1987

H.1.7.3 Environmental Fate and Transport

The predominant anthropogenic source of bromodichloromethane release to the environment is its inadvertent formation during chlorination treatment processes of water. In addition to anthropogenic sources, it is biosynthesized and emitted to the environment by various species of marine macroalgae which are abundant in various locations of the world's oceans. If released to surface water, volatilization will be the dominant environmental fate process. The volatilization half-life from rivers and streams has been estimated to range from 33 minutes to 12 days with a typical half-life being 35 hours. In aquatic regions where volatilization is not viable, anaerobic biodegradation may be the major removal process. Aquatic hydrolysis, oxidation, direct photolysis, adsorption, and bioconcentration are not environmentally important. If released to soil, volatilization is again likely to be the dominant removal process where

exposure to air is possible. Bromodichloromethane is moderately to highly mobile in soil and can therefore leach into groundwaters. If released to air, the only identifiable transformation process in the troposphere is reaction with hydroxyl radicals. The loss of bromodichloromethane through this transformation has an estimated half-life of 6.65 months. This relatively persistent half-life indicates that long-range global transport is possible.

H.1.7.4 Routes of Exposure, Distribution, Absorption, Transport, and Degradation

The general population is exposed to bromodichloromethane through consumption of contaminated drinking water, beverages and food products, through inhalation of contaminated ambient air, and through dermal exposure to chlorinated swimming pool water.

Bromodichloromethane may be absorbed readily by inhalation or ingestion, be distributed widely, preferentially to tissues with high lipid content, and be eliminated in part via expired breath (HSDB, 1993).

A study was performed to determine the absorption, distribution and excretion characteristics of bromodichloromethane in mice and rats. Compounds labeled with carbon-14 were administered by intragastric inoculation to male Spragur-Dawley rats and male B6C3F1 mice. The total radioactivity for sample organs ranged from 3 to 6 percent of the total dose in the rats versus 5 to 14 percent for the mice. The stomach (without contents), nonperfused liver, and kidneys in both rodent species were the organs of highest residual radioactivity levels. In both species the urine contained less than 5 percent of the total radiolabel at 8 hours post incubation and less than 10% of the total radiolabel at 36 to 48 hours. The majority of the compound in both rats and mice was eliminated through the lung in the expired air within 8 hours. BDCM exhibits limited metabolic activation, which was shown by recovery of a higher percentage of the dose as parent compound. Mice metabolize this compound to a greater extent than rats (Mink et al., 1986).

H.1.7.5 Acute Toxicity

Acute toxicity of bromodichloromethane has been investigated in rats and mice. In rats, signs following a single oral dose were sedation, flaccid muscle tone, ataxia, piloerection, and

prostration. Male rats were more susceptible than females to lethal effects. In mice, pathological changes following gastric gavage included fatty infiltration of the liver, and hemorrhaging in the kidneys, adrenals, lung and brain. Males were also more sensitive in mice populations than females (HSDB, 1993).

H.1.7.6 Chronic Toxicity

Both di- and tri-halogenated methane derivatives have been found to produce increased blood levels of methemoglobin. CNS functional disturbances are also reported, including depression of rapid eye movement sleep (HSDB, 1993).

The effects of lifetime exposure to chloroform and bromodichloromethane were studied in Wistar rats. Haloorganic treatment was initiated with weanlings at 2 ml/L chloroform per liter drinking water, or 1.2ml/l bromodichloromethane per liter drinking water. Concentrations of these halomethanes were halved at 72 weeks because of increasing water intake when judged to be moribund or when a large tumor was noted. Sections of liver and other organs with grossly observable lesions were examined histologically. Tumor incidence was also analyzed. Treated rats weighed less than unexposed controls at all ages. At about 15 to 17 weeks, females had a higher consumption of water and halomethanes than males. The incidence of neoplastic nodules was significantly increased in females in either treatment group. Treated females also had a high incidence of hepatic adenofibrosis (Tumasonis et al., 1985)

H.1.7.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Bromodichloromethane was mutagenic in the Ames test using Salmonella typhimurium (TA100 without S-9 activation).

Carcinogenicity

Positive correlations between cancer mortality rates and levels of brominated trihalomethanes in drinking water have been reported in epidemiological studies (HSDB, 1993).

Cultures of human oral carcinoma cell were used to assess the toxicity of halomethanes found in drinking water. Cells were incubated for 72 hours in the presence of 100 to 1000 µg/l. After incubation, viable cells were counted, and concentrations causing 50% inhibition of cell growth (ID50) were determined. A linear dose-response relationship was obtained for bromodichloromethane (Mochida and Yamasaki, 1984).

The National Toxicology Program (1987) reported in that male and female rats given bromodichloromethane by gavage in concentrations ranging from 0.0-0.1 g/kg, there was clear evidence of carcinogenic activity. This was indicated by increased incidence of kidney tubular cell adenomas, kidney tubular cell adenocarcinoma, and large intestine adenomatous polyps. Mice given concentrations ranging from 0.0-0.15 g/kg also demonstrated carcinogenic activity as demonstrated by an increased incidence of kidney adenomas, kidney adenocarcinomas, hepatocellular adenomas, and hepatocellular carcinomas.

Teratogenicity (and other reproductive effects)

No studies were located in the literature regarding the teratogenic or reproductive effects of bromodichloromethane.

H.1.7.8 Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

Bromodichloromethane is a probable human carcinogen (Group B2).

BASIS FOR CLASSIFICATION : Based on inadequate human data and sufficient evidence of carcinogenicity in two animal species (mice and rats) as shown by increased incidence of kidney tumors and tumors of the large intestine in male and female rats, kidney tumors in male mice, and liver tumors in female mice.

EPA Dose-Response Parameters

Carcinogenic effects:

ORAL SLOPE FACTOR : 6.2E-2 per (mg/kg)/day

DRINKING WATER UNIT RISK : 1.8E-6 per (μg/L)

Noncarcinogenic Effects:

Oral RfD Summary:

RfD = 0.02 mg/kg/day

CRITICAL EFFECT/TARGET ORGAN: Renal cytomegaly

UF = 1000. A factor of 100 was employed for extrapolation from animal data and for protection of sensitive human subpopulations. An additional factor of 10 was used because the RfD was based on a LOAEL (although minimally adverse), and to account for data base deficiencies (no reproductive studies).

ORAL RfD MODIFYING FACTOR :

MF = 1

ORAL RfD CONFIDENCE :

Study: Medium

Data Base: Medium

RfD: Medium

Confidence in the study is rated medium because although NTP (1987) incorporated both chronic and subchronic exposures in two species using sufficient numbers of animals and measured multiple endpoints, including histopathology of most organ systems, a NOEL was not determined. Although there are some discrepancies in the dose levels producing adverse effects, there are several published subchronic studies of bromodichloromethane permitting confidence in the data base to be rated medium to low. Thus, overall confidence in the RfD is rated medium to low.

H.1.7.9 References

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H.1.8 Di-n-butylphthalate

H.1.8.1 Background

Di-n-butylphthalate (DBP) is a colorless oily liquid with a very weak aroma. It is used in plasticizing vinyl acetate emulsion systems and in plasticizing cellulose esters. This includes a wide variety of common products such as shower curtains, raincoats, food wraps, car interiors, vinyl fabrics, and floor tiles. DBP is also used an insect repellent, dielectric fluid and hydraulic fluid (Sittig, 1985; Fawell and Hunt, 1988).

H.1.8.2 Pharmacokinetics

There is little information available on the distribution of DBP, although studies have found exposure occurs principally by ingestion of drinking water and food with dermal contact being a minor pathway of exposure (Fawell and Hunt, 1988; ATSDR, 1990). Studies in rats indicate that DBP is extensively absorbed (63 to 97 percent) after an orally administered dose within 24 hours after dosing (ATSDR, 1990). Data suggest that DBP is reasonably well absorbed at a constant rate across the skin (ATSDR, 1990). DBP has demonstrated no significant retention, by ingestion or dermal contact, in any organ after adsorption in rats (ATSDR, 1990).

H.1.8.3 Acute Toxicity

Severe damage to the testes was found in rats given a high oral dose of DBP (2 g/kg/day) for 4 days (Fawell and Hunt, 1988). Lower testes weight, increased liver weight, and severe testicular damage in rats fed 2 percent DBP in the diet for 7 days (Fawell and Hunt, 1988). Histological changes in the testes and slight decreases in kidney weight have also been reported for mice (Fawell and Hunt 1988; ATSDR, 1990). Studies have indicated that LD_{50} in rats and mice is in excess of 20,000 mg/kg (ATSDR, 1990).

H.1.8.4 Chronic Toxicity

Interference with mitochondrial respiration and liver necrosis was noted after long exposure (35 days) to DBP in mice and rats (ATSDR, 1990). No histopathological effects on the kidney, liver or spleen were observed after ingestion of DBP over a 12 month period (Fawell and Hunt, 1988).

Carcinogenicity

Only limited studies have been carried out on the carcinogenicity of DBP. An early investigation did not detect any carcinogenic effects in rats exposed from three to five generations in duration (Fawell and Hunt, 1988). There is sufficient evidence to suggest that di-ethyl hexyl phthalates (DEHP) causes hepatocellular carcinomas in rats and mice (ATSDR, 1990). Since DEHP is a powerful peroxisome proliferator, which is believed to be an important aspect of the carcinogenic response; it may raise the possibility that DBP, also a peroxisome proliferator, could be carcinogenic in rodents, although no such evidence exists (ATSDR, 1990).

Mutagenicity

DBP has tested negative or marginally positive in gene mutation and chromosomal aberration studies (ATSDR, 1990). It has been reported that DBP was weakly mutagenic in vitro to Salmonella typimurium TA100 in liquid suspension assays (Fawell and Hunt, 1988). The significance of these findings to mammalian organism is not known because no in vivo gentoxicity studies have been conducted (ATSDR, 1990).

Reproductive/Developmental Effects

Decreased testes weight, decreased number of spermatocytes and degeneration of the seminiferous tubules of the testes are some of the effects on the reproductive system of male rats and guinea pigs after exposure to high doses of DBP (ATSDR, 1990). DBP also had adverse effects on reproduction in female rates. Increases in fetal and neonatal mortality was observed at doses of about 1,000 mg/kg/day. Ingestion of higher doses of DBP resulted in a decrease in placental weight, subcutaneous edema, hemorrhages, and kidney damage effects (Fawell and Hunt, 1988). Due to limited and inconsistent data, it is not possible to judge conclusively whether DBP is a teratogen or not (ATSDR, 1990).

Sensitive Populations

At present, there is no data to suggest that any segment of the human population is unusually susceptible to the effects of di-n-butylphthalate (ATSDR, 1990).

Chemical Interactions

No information is available regarding the interaction of DBP with other chemicals.

Dose-Response Parameter Estimates

The dose-response parameter estimates for carcinogens and noncarcinogens are computed differently by the EPA; therefore, these estimates are presented separately below.

Carcinogenic Effects:

Di-n-butylphthalate is not classified as a carcinogen (Group D) by the EPA. The EPA has not derived an estimate of the dose-response relationship. Therefore, the carcinogenicity of di-n-butylphthalate was not quantitatively evaluated in this assessment.

Noncarcinogenic Effects:

The Office of Health and Environmental Assessment has derived a chronic oral reference dose (RfD) for di-n-butylphthalate of 0.1 mg/kg/day (USEPA, 1991) based on the mortality of male rats fed upper dosages of 1.25% dibutyl phthalate for a period of one year (Smith, 1953). A factor of 10 each was applied to account for interspecies variation, protection of sensitive human subpopulations, and for both the less-than-chronic duration of the study and deficiencies in the study (USEPA, 1991). An inhalation reference dose is not available for dibutyl phthalate.

Oral Reference Dose: 0.1 mg/kg/day (USEPA, 1991).

H.1.8.5 References

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H.1.9 Ethylbenzene

H.1.9.1 Occurrence and Use

Ethylbenzene is a volatile organic compound principally produced as a manufacturing byproduct in the refining of petroleum products. Ethylbenzene is commercially used in the manufacturing of acetophenone and styrene, and as a constituent of asphalt, naphtha, gasoline, aviation fuels, and as a general solvent for resins (Fawell and Hunt, 1988). The chemical is also a component of cigarette smoke condensate, and has been detected in human respiratory air in higher concentrations in smokers than in nonsmokers (Clayton and Clayton, 1981).

Brodzinsky and Singh (1982) report median urban/suburban atmospheric ethylbenzene concentration of 5.2 mg/m^3 and a median rural/remote concentration of 2 mg/m^3. Ethylbenzene is a priority pollutant that is one of the 25 most frequently found compounds in industrial and municipal discharges and is detected in drinking water in the very low mg/l range (EPA, 1985).

H.1.9.2 Physical and Chemical Properties of Ethylbenzene

Molecular Weight	106.17[1]
Water Solubility, mg/l	1.5E+02[2]
Vapor Pressure, mm Hg	7.0E+00[2]
Henry's Law Constant, atm-m^3/mole	6.4E-03[3]
Octanol-Water Partition Coefficient	1.4E+03[2]
Organic Carbon Partition Coefficient	1.1E+03[4]
Bioaccumulation Factor for Fish	1.5E+02[1]
Bioaccumulation Factor for Shellfish	2.7E+01[1]

Sources: [1]MEPAS, 1989
[2]USEPA, 1984
[3]ICF, 1987
[4]Mabey, et al. 1982

H.1.9.3 Environmental Fate and Transport

Ethylbenzene will enter the atmosphere primarily from fugitive emissions and exhaust connected with its use in gasoline. More localized sources will be emissions, wastewater and spills from its production and industrial use. If ethylbenzene is released to the atmosphere, it exists predominantly in the vapor phase based on its vapor pressure where it will photochemically degrade by reaction with hydroxyl radicals (half-life 0.5 to 2 days), and partially return to the earth in rain. It will not be subject to direct photolysis. Releases into water will decrease in concentration by evaporation and biodegradation. The time for this decrease and the primary loss processes will depend on the season, and the turbulence and microbial populations in the particular body of water. Representative half-lives are several days to 2 weeks. Some ethylbenzene may be adsorbed by sediment by significant bioconcentration in fish is not expected to occur based upon its octanol/water partition coefficient. Ethylbenzene is only adsorbed moderately by soil. It will not significantly hydrolyze in water of soil (HSDB, 1993).

H.1.9.4 Pharmacokinetics: Routes of Exposure, Distribution, Absorption, Transport, and Degradation

The primary source of exposure for the general population is ambient air, especially in areas of high traffic. However, exposure from drinking water is not uncommon (HSDB, 1993).

In a study of human volunteers exposed to varying levels of airborne ethylbenzene (100 to 370 mg/m^3), the mean absorption efficiency from the respiratory tract was 64 percent (Bardodeji and Bardodejova, 1970). Pulmonary absorption of ethylbenzene in rats has previously been estimated at 44 percent (Chin et al., 1980). No quantitative data is available on the absorption efficiency of ethylbenzene from the gastrointestinal (GI) tract, but it is believed to be approximately 100 percent (Fawell and Hunt, 1988). In a laboratory inhalation study with rats, ethylbenzene, once absorbed, was rapidly distributed throughout the body with the highest concentrations found in the digestive tract, adipose tissue, lung, and kidneys (Chin et al., 1980). Tissue levels were significantly lower after 42 hours illustrating rapid excretion. Metabolic conversion of ethylbenzene is rather complex, with metabolites such as mandelic acid, 1-phenylethanol, phenylglyoxylic acid and 2-ethylphenol commonly detected in the urine of exposed humans

(Fawell and Hunt, 1988). Mandelic acid and phenylglyoxylic acid account for approximately 70 and 20 percent of the urinary metabolites found in exposed humans, respectively. As indicated above, elimination of ethylbenzene is rapid with greater than 95 percent of ethylbenzene eliminated in urine of exposed humans within 24 hours (EPA, 1985).

H.1.9.5 Acute Toxicity

Ethylbenzene is primarily an irritant of cellular membranes, which may lead to erythema (redness of skin) and skin blistering (Fawell and Hunt, 1988). Humans exposed to 5,000 ppm of ethylbenzene for only a few seconds experience an intolerable irritation of nose, eyes, and throat (Fawell and Hunt). Eye irritation was found to diminish after a few minutes at 1,000 ppm. However, the predominant toxic effects from inhalation exposures are directed on the liver (increased liver microsomal enzyme activity) and kidney (increased weight and enzyme activity) as well as an anesthetic and narcosic effect exerted on the central nervous system (EPA, 1985). The oral LD_{50} in rats (Carwor-Wistar) was 5.5 g/kg (Smyth et al., 1962).

H.1.9.6 Chronic Toxicity

There does not appear to be much human data on chronic ethylbenzene exposure, but workers exposed to 100 ppm complained of CNS abnormalities (fatigue, sleepiness, and headaches) and mild irritant effects on the eyes and respiratory tract (Proctor et al., 1988). In several Russian studies of questionable quality, cellular and biochemical effects (leukocytosis, decreased number of lymphocytes, decreased serum albumin and decreased globulin proteins) were noted in humans exposed to ethylbenzene vapors at 100 and 1,000 mg/m^3 for 4 hours per day for 7 months (the number of days/week not specified) (EPA, 1985). Rats administered ethylbenzene orally 5 days/week for 6 months experienced histopathological changes and increases in liver and kidney weights at doses of 408 and 680 mg/kg/day (Wolf et al., 1956). No effects were noted at lower doses. In inhalation studies, slight toxic effects (increased liver and kidney weights) were observed in rats exposed to 400 ppm 7 days/week for 6 months, while no effects were noted in rabbits, guinea pigs, and monkeys similarly exposed (Wolf et al, 1956).

H.1.9.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

At 0.4 mg/plate, ethylbenzene was not mutagenic in the Ames assay with or without metabolic activation, using several strains of Salmonella (Nestman et al., 1980). It was also negative for gene mutations in Salmonella Typhimurium, E. Coli, and Saccharomyces Cerevisiae (EPA, 1991). Also, ethylbenzene did not cause chromosomal damage in rat liver cells (Fawell and Hunt, 1988). In contrast, ethylbenzene hydroperoxide was positive with metabolic conversion in gene conversion test systems using E. Coli and yeast (EPA, 1991).

Carcinogenicity

At this time, no studies appear to be available on the carcinogenicity of ethylbenzene. However, the National Toxicology Program is currently evaluating the carcinogenicity of ethylbenzene (EPA, 1991). As such, the EPA has categorized ethylbenzene as a group D carcinogen (not classifiable as to human carcinogenicity((EPA, 1991).

Teratogenicity (and other reproductive effects)

A study by Tatrai and coworkers suggested that ethylbenzene has some embryotoxic and teratogenic activity (Tatrai et al., 1982). Rats inhaling 600, 1200,or 2400 mg ethylbenzene/m^3 for 24 hr/day from days 7-15 of pregnancy showed mild toxicity. The highest dose retarded skeletal development and weight gain in the fetuses and increased the incidence of extra ribs. Sacral displacement with abnormal development was observed in 2 instances.

H.1.9.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

The Carcinogen Assessment Group (CAG) has classified ethylbenzene in Group D - Not Classified as to human carcinogenicity based on a lack of animal bioassays and human studies (USEPA, 1992).

EPA Dose-response Parameters

ORAL RfD : 1E-1 mg/kg/day

CRITICAL EFFECT/TARGET ORGAN : Liver and kidney toxicity

ORAL RfD UNCERTAINTY : UF = 1000.

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

ORAL RfD MODIFYING FACTOR : MF = 1.

ORAL RfD CONFIDENCE :

Study: Low

Data Base: Low

RfD: Low

Confidence in the chosen study is low because rats of only one sex were tested and the experiment was not of chronic duration. Confidence in the supporting data base is low because other oral toxicity data were not found. Low confidence in the RfD follows.

INHALATION RfD : 1E+0 mg/cu.m

CRITICAL EFFECT/TARGET ORGAN : Developmental toxicity

INHALATION RfD UNCERTAINTY : UF = 300

The uncertainty factor of 300 reflects a factor of 10 to protect unusually sensitive individuals, 3 to adjust for interspecies conversion and 10 to adjust for the absence of multigenerational reproductive and chronic studies.

INHALATION RfD MODIFYING FACTOR: MF = 1.

INHALATION RfD CONFIDENCE :

Study: Low

Data Base: Low

RfC: Low

The developmental study by Hardin et al. (1981) was well-conducted and indicated no clearly adverse effects in any species. The study is given a low confidence rating because higher exposure levels may have provided more information on the potential for maternal toxicity and developmental effects. The data base is given a low rating since although other studies have examined a variety of other endpoints (e.g., liver and lung), by histopathology in rats and mice, there are no chronic studies and no multi-generation developmental studies. These latter studies would be useful to determine more conclusively the potential of ethylbenzene to affect development. NTP does not consider observations of lung lesions in rats exposed in the NTP subchronic study to be treatment-related. However, no infectious agent has been detected. Therefore, there remains a possibility that ethylbenzene may play a role in producing lung lesions. It is anticipated that this issue will be clarified upon completion of the chronic study in progress. In view of the previous considerations, the RfC is given a low confidence rating.

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H.1.10 Lead

H.1.10.1 Occurrence and Use

Lead (Pb) is a major environmental contaminant and one of the most common pollutants at hazardous waste sites. Combustion of gasoline is the major source of lead, as well as being a component of automotive batteries and paint.

Air emissions from combustion sources and lead paint are the primary anthropogenic sources of environmental lead.

H.1.10.2 Physical and Chemical Properties of Lead

Lead is a gray-white metal of silvery luster that has a low melting point (327.5°C) and a boiling point of 1740°C. The metal is soft, malleable and ductile, a poor electrical conductor and highly impervious to corrosion. A listing of the solubilities and physical properties of the more common compounds of lead is given in Weast 1982 and EPA 1986a. Most inorganic lead salts are sparingly soluble (eg., PBF_2, $PbCl_2$) or virtually insoluble ($PbSO_4$, $PbCrO_4$) in water; the notable exceptions are lead nitrate, $PB(NO_3)_2$ and lead acetate, $Pb(OCOCH_3)_2$. Inorganic lead (II) salts are, for the most part, relatively high-melting-point solids with correspondingly low vapor pressures at room temperatures. The vapor pressures of the most commonly encountered lead salts are also tabulated in EPA 1986a.

Molecular Weight	207.00[1]
Water Solubility, mg/l	0.0E+00[2]
Bioaccumulation Factor for Fish	1.0E+02[3]
Bioaccumulation Factor for Shellfish	1.0E+02[3]

Sources: [1]Multi-Media Exposure Assessment Manual, 1989
[2]Weast, 1979
[3]Napier et al., 1980

H.1.10.3 Environmental Fate and Transport

Although the chief source of environmental exposure is the atmosphere, Pb enters the soil and water as fallout. Lead deposited on soils can bind to a number of other naturally occurring materials, including other dusts, clays, hydrous oxides and humic and fulvic acids. Once it pollutes the soil, opportunities are enhanced for lead to be absorbed and recycled into the human food chain through grazing animals, home gardening and general agricultural activity. The greatest concentrations of Pb have been found close to heavily travelled roads. Lead enters the human body via inhalation and ingestion.

At one time, automobile exhaust accounted for about 90% of all air emissions in the United States; the recent phase-down of lead content of gasoline and reductions in usage of leaded gasoline have, and will continue to, substantially decrease the contribution of automobile exhaust to air lead (EPA 1986b). Lead in automobile exhaust originates from the combustion of gasoline containing organic lead additives, primarily tetraethyl and tetramethyl lead. Lead is emitted from vehicles primarily as particles of inorganic lead, with a small percentage as volatile lead alkyls.

Lead released to the air deposits on terrestrial surfaces and enters the soil, where it can have several possible fates. Lead can be retained in organic complexes near the soil surface. For example, insoluble lead species may be free or adsorbed on solid inorganic or organic matrices. Studies of lead/soil interactions show that soil fixation of lead is mainly affected by pH, cation exchange capacity and organic matter content of soil. Lead appears most strongly associated with soil organic carbon fraction. If little or no organic material is in the soil, other components can regulate lead fixation. These include hydrous manganese oxide (Forstner, et al., 1981) and hydrous ferric oxide (Swallow, et al., 1980). Levels of lead in rural soils, away from industrial emissions and roadbeds, range from 5-30 μg lead/g soil (see Table 1). Levels of lead near roadbeds can be much larger (30-2000 μg/g) and will vary with past and present traffic density and vehicle speed (Page and Gange 1970; Quarles, et al., 1974; Wheeler and Rolfe 1979). Much higher levels (greater than 30,000 μg/g) can occur in the immediate vicinity of industrial sources (Yankel, et al., 1977; EPA 1986b). Lead bound to organic constituents in soil can remain in soil

for long periods of time. As a result, elevated levels can persist long after sources of deposition have been reduced (Prpic-Majic, et al., 1984).

Dust is an important source of oral lead intake in infants and children. The term "dust" refers to house and outdoor dust; house dust is dust in the interior of buildings and includes such things as material from fabrics (carpet) and paint and soil tracked or blown into the house. Outdoor dust includes anthropogenic materials deposited on outside surfaces, referred to as "street dust," and the mobile uppermost layer of natural soil, referred to as "soil dust" (EPA 1986b). Outdoor dusts can be transported by wind and rain runoff (Laxen and Harrison 1977). Lead persistence in dust depends on the amount and size of particles; big particles tend to persist in air longer than smaller ones. Levels in outdoor dust near point sources have been shown to decline within 1-2 years after atmospheric emissions decreased (Morse, et al., 1979; Prpic-Majic, et al., 1984).

Lead can enter ambient water from atmospheric deposition and surface runoff, where it tends to form insoluble salts and precipitates. Concentrations of lead in US ambient waters are typically low. Mean values tend to be less than 3-28 µg/l (NAS 1980; EPA 1986b). In contrast to ambient water, levels in drinking water can be much higher (10-1,000 µg/l) because of leaching of lead from lead pipe and leaded solder joints. Lead concentrations in drinking water vary with the amount of lead in the household plumbing and corrosiveness of the water. Soft or acidic waters tend to be more corrosive and promote higher concentrations of dissolved lead in the drinking water (Worth, et al., 1981). Drinking water can be a major source of lead intake for infants and young children who consume large amounts of infant formula prepared with household water.

H.1.10.4 Routes of Exposure, Absorption, Distribution, Transport, and Degradation

Oral intake, rather than inhalation, is generally the predominant route of intake for humans. Intake occurs through ingestion of food and beverages, and in infants and children, through ingestion of dust and soil.

Ingestion of lead-based paint is one of the most frequent causes of severe lead intoxication in children (Chisolm 1984). Although the US Consumer Product Safety Commission banned the use

of household paints containing greater than 0.06% lead in 1977, the hazard persists in homes and apartments constructed before the ban. Infants and children can be exposed to lead in paint from ingesting and inhaling house dust contaminated with paint dust and from intentionally ingesting paint chips (paint pica). Exposure can occur outside the house from ingestion of street and soil dust.

Absorption of ingested lead is quantitatively the most significant route of uptake of inorganic lead in most human populations; the exception is occupational exposures in which inhalation of airborne lead results in significant uptake. Percutaneous absorption (ie., dermal uptake) is not considered a significant route of absorption of inorganic lead.

Alkyl lead compounds (e.g., triethyl, trimethyl, tetraethyl and tetramethyl lead) are more highly lipophilic than inorganic lead and are readily absorbed from the lung and skin.

For inhalation, amounts and patterns of deposition of particulate aerosols in the respiratory tract are affected by the size of the inhaled particles, age-related factors that determine breathing patterns (e.g., nose breathing vs mouth breathing), airway geometry and airstream velocity within the respiratory tract. Estimates for fractional absorption of large particles (greater than 2.5 um) deposited in the upper respiratory tract range from 40-50% (Kehoe, 196la,b,c; Chamberlain and Heard, 1981).

Chamberlain, et al., (1978) exposed adult human subjects to radioactive lead in engine exhaust, lead oxide or lead nitrate (less than 1 um particle size) and observed that 90% of the deposited lead was cleared from the lung within 14 days. Morrow, et al., (1980) reported 50% absorption of deposited lead inhaled as lead chloride or lead hydroxide within 14 hours. An analysis of the radioisotopic dilution studies of Rabinowitz, et al., (1977) in which adult human subjects were exposed daily to ambient air lead indicated that about 90% of the deposited lead was absorbed daily (EPA 1986b).

Quantitative analyses of the relationship between aerosol particle size and deposition in the human respiratory tract have been combined with information on size distributions of ambient air lead aerosols to estimate deposition and absorption efficiencies for inhaled lead in adults and children (EPA 1986b; Cohen 1987). It was estimated that 38% of the inhaled lead in adults living in the vicinity of an industrial source is absorbed. For some urban and rural atmospheres, where submicron particles dominate the airborne lead mass, the estimated fractional absorption is 15-30% (Cohen, 1987).

The retention and absorption of gaseous tetraethyl and tetramethyl lead has been examined in volunteers who inhaled radioactively-labelled tetraalkyl lead (Heard, et al., 1979). Initial lung retention was 37 and 51% for tetraethyl and tetramethyl lead, respectively. Of these amounts, 40% of tetraethyl lead and 20% of tetramethyl lead was exhaled within 48 hours; the remaining fraction (tetraethyl, 60%; tetramethyl, 80%) was absorbed.

The gastrointestinal tract is the primary site of absorption of lead in children and most adult populations, with the exception of those subject to occupational exposure (EPA 1986b). Gastrointestinal absorption of lead varies with age, diet and nutritional status as well as the chemical species and particle size of the ingested lead. Dietary balance studies have yielded estimates ranging from 7-15% for gastrointestinal absorption in adults (Kehoe, 1961 a,b,c; Chamberlain, et al., 1978; Rabinowitz, et al., 1980). Gastrointestinal absorption of dietary lead is greater in infants and children than in adults. A mass balance study in infants aged 2 weeks to 2 years yielded estimates of 42% for children with dietary intakes of greater than or equal to 5 μg PB/kg body weight. Lower dietary intakes were associated with highly variable absorption (Ziegler, et al., 1978). A study conducted with infants and children aged 2 months to 8 years (daily intake, 10 μg Pb/kg body weight) yielded estimates of 53% for gastrointestinal absorption (Alexander, et al., 1973). Individuals with poor nutritional status may absorb more lead from environmental sources (EPA, 1986b).

Inorganic lead is not readily absorbed through the skin (percutaneous absorption). Values of 0-0.3% of the administered dose were reported for humans exposed to dermal applications of cosmetic preparations containing lead acetate.

Mineralized tissues (eg., bone and teeth) are the single largest pool for absorbed lead, accounting for about 95% of the total lead burden in adults and slightly less in children (Barry 1975, 1981). Lead not contained in mineralized tissue is distributed in soft tissues, primarily blood, liver and kidneys. Small amounts accumulated in other soft tissues such as brain, although not quantitatively significant to the overall distribution of the body burden, are of considerable toxicological importance. Lead readily transfers across the placenta and distributes to fetal tissues (Horiuchi, et al., 1959; Barltrop, 1959; Lauwerys, et al., 1978; Kovar, et al., 1984; Tsuchiya, et al., 1984; Korpela, et al., 1986). Lead distributes to a variety of tissues after exposure to lead alkyls. Levels of lead in humans that have been exposed to tetraethyl and tetramethyl lead are highest in liver followed by kidney and brain (Bolanowska, et al., 1967; Grandjean and Nielsen 1979).

Metabolism of inorganic lead consists primarily of reversible ligand reactions including the formation of complexes with amino acids and nonprotein thiols and binding to various complexes with amino acids and nonprotein thiols and binding of various cellular proteins (Bruenger, et al., 1973; Raghavan and Gonick, 1977; Everson and Patterson 1980; Ong and Lee 1980; DeSilva 1981). Tetraethyl and tetramethyl lead undergo oxidative dealkylation to the corresponding trialkyl derivatives that are thought to be the neurotoxic forms of these compounds. Dealkylation of tetralkyl lead occurs in a variety of species, including humans (EPA 1986b).

H.1.10.5 Acute Toxicity

Acute lead-induced nephrotoxicity is characterized by proximal tubular nephropathy of the kidney. Characteristic lesions described in both humans and animals include nuclear inclusion bodies and mitochondrial changes in the epithelial cells of the pars recta of the proximal tubule and impaired solute reabsorption (eg., glucose, amino acids, phosphate) of the kidney. Acute nephrotoxicity has been observed in children with lead encephalopathy and is associated with

relatively high blood lead levels (ie., greater than 80 µg/dl) (Chisolm, et al., 1955; Chisolm 1962, 1968; Pueschel, et al., 1972; EPA 1986b).

H.1.10.6 Chronic Toxicity

Lead Neurotoxicity in adults: Severe lead neurotoxicity is characterized by overt symptoms of irritability, shortening of attention span, headache, muscular tremor, peripheral neuropathy, abdominal pain, loss of memory and hallucinations. Delirium, convulsions, paralysis and death can also occur. In adults, some of these overt symptoms may become apparent at blood lead levels in the range of 40-60 µg/dl (EPA 1986b). Nonovert symptoms of neurotoxicity associated with lead exposure in adults include impaired performance on psychomotor tests, decreased nerve conduction velocity and impaired cognitive function. Blood lead levels associated with these effects range upwards from 30 µg/dl (EPA 1986b).

Lead Neurotoxicity in Children: Symptoms of overt neurotoxicity in children are similar to those observed in adults. Nonovert symptoms of neurotoxicity that have been reported in children include impairments or abnormalities in psychomotor and cognitive function. Severe psychomotor and cognitive deficits appear to be associated with blood lead levels at the range of greater than or equal to 40-60 µg/l in "high-risk" populations of children (EPA 1986b). High risk populations include children with previous histories of lead encephalopathy or paint pica and children with possible occupational exposure (eg., lead pottery manufacture).

Several large-scale studies (EPA 1986b) reported effects on mental development and cognitive ability associated with blood lead levels greater than or equal to 10-15 µg/dl.

An inverse linear association between Stanford-Binet IQ scores and contemporary blood lead levels was seen over the entire range of 6-47 µg/dl in a study of uniformly low socioeconomic status black children, 3-7 years old (Hawk, et al., 1986; Schroeder and Hawk, 1987). A study of 6-9-year old children in Edinburgh, Scotland, also indicated a negative linear correlation between

blood lead and scores on tests of cognitive ability (Fulton, et al., 1987). The correlation extended across a range of 5-22 µg/dl mean blood lead levels.

A nerve conduction velocity study in children (aged 5-9 years) living in the vicinity of a lead smelter (Schwartz, et al., 1988) indicated a threshold for decreased maximal nerve conduction and estimated it to be within the range of 20-30 µg/dl.

Effects of Lead on Heme Biosynthesis and Erythropoiesis: Lead interferes with heme biosynthesis by decreasing the activity of enzymes in this pathway (EPA 1986b). Significant impairment of hemoglobin synthesis occurs in adults only at relatively high blood levels. The threshold for a decrease in blood hemoglobin in adults and children is achieved at a blood lead level of 50 µg/dl (Meredith, et al., 1977; Fischbein, 1977; Alvares, et al., 1975). Frank anemia in adults has been associated with levels greater than 80 µg/dl (Tola, et al., 1973; Grandjean 1979; Lilis, et al., 1978; Wada, et al., 1973; Baker, et al., 1979). Available information indicates the potential for undesirable effects on heme biosynthesis and erythroblast pyrimidine metabolism in children with blood lead levels greater than 10-15 µg/dl and possibly at lower levels (EPA 1990a).

Effects of Lead on the Kidney: Chronic toxicity in the kidney is characterized by interstitial fibrosis and decreased glomerular filtration rate (Goyer 1982; EPA 1986b, ATSDR/EPA 1988). Chronic nephropathy, indicated by nuclear inclusion bodies, mitochondrial changes, interstitial fibrosis and glomerular changes, have been associated with prolonged (greater than 10 years) occupational exposures and blood lead levels greater than 40-60 µg/dl (Lilis, et al., 1968; Cramer, et al., 1974; Biagini, et al., 1977; Wedeen, et al., 1975, 1979; Buchet, et al., 1980; Hong, et al., 1980).

Effects of Lead on Blood Pressure: The relationship between concurrent blood lead levels and blood pressure in adults has been examined in several epidemiological studies (Pocock, et al., 1984, 1985, 1988; Harlan, et al., 1985; Pirkle, et al., 1985; Landis and Flegal 1987; Elwood, et al., 1988 a, b; Neri, et al., 1988; Sharp, et al., 1988; Weiss, et al., 1988; Moreau, et al., 1988). The weight of evidence provided by the several large- and small-scale epidemiology studies supports

the existence of a positive correlation between blood lead level and blood pressure. In addition, the results of numerous animal studies support a dose-response relationship between lead exposure and elevated blood pressure. Chronic exposure to inorganic lead increases blood pressure in laboratory animals (Victery 1988). The correlation between blood lead levels and blood pressure in humans appears to extend to blood lead levels less than 20 μg/dl and possibly to as low as 7 μg/dl. This suggests that as blood lead level increases greater than 7 μg/dl to levels greater than or equal to 20 μg/dl, the risk for increased blood pressure increases.

Effects of Lead on Serum Vitamin D Levels: Serum levels of 1,25-dihydroxycholecalciferol are inversely correlated with blood lead in children (Rosen, et al., 1980; Mahaffey, et al., 1982). The correlation persists when examined across a range of blood lead levels extending from 12-60 μg/dl; however, the dose-effect relationship has not been characterized. Based on a linear regression analysis of data on serum 1,25-dihydroxycholecalciferol and blood lead levels in children as well as data on 1,25-dihydroxycholecalciferol levels in other vitamin D related clinical disorders in children, it has been predicted that increasing the blood lead levels from 12-60 μg/dl will lower serum 1,25-dihydroxycholecalciferol to clinically adverse levels (Mahaffey, et al., 1982). Chronic depression of 1,25-dihydroxycholecalciferol levels of a much smaller magnitude than that associated with frank clinical disorders of calcium and phosphate metabolism have the potential to alter bone development and growth in children; therefore, blood lead levels greater than 12 μg/dl should be considered potentially undesirable with respect to changes in 1,25-dihydroxycholecalciferol levels in children. 1,25-dihydroxy-cholecalciferol, the active form of vitamin D; is a hormone that plays an important role in the regulation of gastrointestinal absorption and renal excretion of calcium and phosphorus and in the mineralization of bone. Deficiencies in 1,25-dihydroxy-cholecalciferol are associated with decreased bone mineralization and clinical syndrome of rickets in children. 1,25-dihydroxy-cholecalciferol may also stimulate gastrointestinal absorption of lead (Smith, et al., 1978).

H.1.10.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Structural chromosomal aberrations and increased sister chromatid exchanges in peripheral lymphocytes have been associated with chronic exposure to lead resulting in blood lead levels in the range of 24-89 μg/dl, although effects were not observed over this range of blood levels in numerous studies (EPA 1986b). Studies reviewed by EPA (1989b) demonstrated that lead compounds induce cell transformation in mouse cells and rat embryo cells infected with the Rauscher murine leukemia virus.

Carcinogenicity

Epidemiological studies of industrial workers, where the potential for lead exposure is usually greater than for a "normal population," have been conducted to evaluate the role of lead in the induction of human neoplasia (Cooper 1976, 1981; Cooper and Gaffey 1975; Chrusciel 1975; Dingwall-Fordyce and Lane 1963; Lane 1964, McMichael and Johnson 1982; Neal, et al., 1941; Nelson, et al., 1982). Two studies (Dingwall-Fordyce and Lane 1963 and Nelson, et al., 1982) did not find any association between exposure and cancer mortality. Selevan, et al., (1984), in their retrospective cohort mortality study of primary lead smelter workers, found a slight decrease in the total cancer mortality compared to controls. Apparent excesses were observed for respiratory cancer and kidney cancer. Cooper and Gaffey (1975) and Cooper (1985) performed a cohort mortality study of battery plant workers and lead smelter workers. They found statistically significant excesses for total cancer mortality, stomach cancer and lung cancer in the battery plant workers. Although similar excesses were observed in the smelter workers, they were not statistically significant. Cooper and Gaffey (1975) felt it was possible that individual subjects were monitored primarily on the basis of obvious signs of lead exposure, while others who showed no symptoms of lead poisoning were not monitored.

In general, these studies made no attempt to consider types of lead compounds to which workers were exposed or to determine probable routes of exposure as well as information on the possible contribution from smoking. All studies also included exposures to other metals such as arsenic, cadmium (both known carcinogens) and zinc for which no adjustment was done. The cancer excesses observed in the lung and stomach were relatively small. There was no consistency of site among the various studies and no study showed any dose-response relationship. Thus, the

available human evidence is considered to be inadequate to refute or demonstrate any potential carcinogenicity for humans from lead exposure.

In animals, the carcinogenic potential of lead salts (primarily phosphates and acetates) administered via the oral route or by injection has been demonstrated in rats and mice by more than 10 investigators (Zollinger 1953; Boyland, et al., 1962; Van Esch, et al., 1962; Baldwin, et al., 1964; Balo, et al., 1965; Hass, et al., 1967; Mao and Molnar 1967; Epstein and Mantel 1968; Zawirska and Medras 1968; Van Esch and Kroes 1969; Zawirska and Medras 1972; Azar, et al., 1973; Furst, et al., 1976; Koller, et al., 1985). The most characteristic cancer response is bilateral renal carcinoma. Rats given lead acetate or subacetate orally have developed gliomas and lead subacetate also produced lung adenomas in mice after intraperitoneal administration. Most of these investigations found a carcinogenic response only at the highest tolerated doses. The lead compounds tested in animals are almost all soluble salts. Metallic lead, lead oxide and lead tetralkyls have not been tested adequately. Studies of inhalation exposure have not been located in the literature (EPA 1993).

Teratogenicity (and other reproductive effects)

Severe occupational exposure to lead has been associated with increased incidence of spontaneous abortion (EPA 1986b) in exposed women. In the Port Pirie cohort study, pregnancy outcome in populations near and distant from a lead smelter indicated that the risk for pre-term delivery was positively related to maternal blood lead, over a range of 8-32 µg/dl (McMichael, et al., 1986). Depressed sperm production and development has been associated with occupational exposure to lead. Based on studies by Lancranjan, et al., 1975 and Wildt, et al., 1983, the EPA concluded that undesirable effects on sperm or testes may occur in men as a result of chronic exposures leading to blood lead levels of 40-50 µg/dl (EPA 1986b).

The effects of prenatal and neonatal lead exposure on perinatal status and postnatal mental and motor development have been examined in several epidemiologic studies. Four prospective studies initiated in the cities of Boston, Cincinnati, Cleveland and Port Pirie, Australia, are notable (Bellinger, et al., 1987 a,b, 1989; Dietrich, et al., 1987, 1989; Ernhart, et al., 1986; McMichael, et al., 1986; Vimpani, et al.,1985; Baghurst, et al., 1987). Based on an extensive

evaluation of these studies, the EPA concluded that "all of these studies taken together suggest that neurobehavioral deficits, including declines in Bayley Mental Development Index (MDI) scores and other assessments of neurobehavioral function, are associated with prenatal blood lead exposure levels on the order of 10-15 μg/dl, and possibly even lower, as indexed by maternal or cord blood lead concentrations" (EPA 1986b).

H.1.10.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

The EPA has classified lead as a probable human carcinogen (Class B2). This classification is based on the observation of increased kidney cancer in rats and mice, and on increases in tumors in rats.

EPA Dose-Response Parameters (IRIS, 1994)

Carcinogenic Effects:

The EPA has not derived an oral and inhalation cancer potency factors for lead (EPA 1993).

Noncarcinogenic Effects:

Dose-response estimates for oral and inhalation exposures are not available for the noncarcinogenic effects of lead (IRIS, 1994). An old RfD for non-cancer effects is available for the non-cancer impacts of lead exposure on humans. It is 1.0E-03 mg/kg-day. However, the EPA has determined that an RfD would not be appropriate to protect children from adverse developmental impacts of lead exposure due to the complex relationship between lead exposures by various routes, blood-lead levels, and the occurrence of adverse effects. Instead, EPA had developed a biokinetic model for assessing the impacts of multi-route lead exposures on childrens' blood-lead levels (EPA 1990b) and recommends that it be used to evaluate the health significance of lead exposures, using a target blood lead level of 10 μg/dl as an indicator of potential adverse effects. This model applies to infants and young children (0 to 6 years old).

H.1.10.9 References

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H.1.11 Mercury

H.1.11.1 Occurrence and Use

Mercury (Hg) heavy metal which can exist in three forms: elemental, inorganic and organic compounds. There are both natural and anthropogenic sources of mercury, including normal degassing of the earth's crust, mining, smelting, industrial discharge, paper pulp industries, pesticides and the burning of fossil fuels. As much as one third of atmospheric mercury may be due to industrial release of organic and inorganic forms.

H.1.11.2 Physical and Chemical Properties of Elemental Mercury

Molecular Weight	201.00[1]
Water Solubility, mg/l	0.0E+00[2]
Vapor Pressure, mm Hg	2.0E-03[3]
Bioaccumulation Factor for Fish	2.0E+05[4]
Bioaccumulation Factor for Shellfish	2.0E+05[4]

Source: [1]Multi-Media Exposure Assessment Manual, 1989
[2]Weast, 1979
[3]EPA, 1981
[4]Napier et al., 1980

H.1.11.3 Environmental Fate and Transport

Methyl mercury which is formed in sediments following industrial discharge of mercury has been shown to cause serious deleterious effects to both human health and the environment because of its ability to bioaccumulate. Methyl mercury is stable in the aquatic environment and is taken up by fish in the food chain, which may eventually result in exposure to humans. A very famous outbreak of methyl mercury poisoning occurred in the Minamata Bay area of Japan, where mercury containing effluent from a vinyl chloride production process emptied into the bay from a nearby factory, causing contamination of fish and shellfish. Humans and animals eating fish experienced central nervous system disorders characterized by degeneration and death of nerves in the focal areas of the cerebral cortex (i.e. the largest part of the brain), loss of vision, speech

impairment, and deafness. In the United States, there is concern over contamination of Mercury in the region of the Great lakes.

H.1.11.4 Routes of Exposure, Absorption, Distribution, Transport, and Degradation

Exposure from soil and water may either be to elemental, inorganic, or organic mercury compounds. For exposure to biota or sediments under reducing (oxygen deficient) conditions, exposure to the more toxic organic species are generally predominant. Principle routes of exposure include atmospheric via the inhalation of elemental mercury vapor, and ingestion of methyl mercury in water and food. In humans, elemental and inorganic mercury compounds are efficiently absorbed following inhalation exposure but poorly absorbed following oral exposure (EPA, 1984). Once absorbed, mercury is generally distributed about the body, binding to the sulfhydryl groups of many proteins. Mercury is excreted in the urine and feces. Small quantities go into the hair and other routes, including the exhaling of some elemental mercury (Carson et al., 1987).

H.1.11.5 Acute Toxicity

Acute mercury poisoning is usually caused by the soluble inorganic salts. Early signs and symptoms include pharyngitis, dysphagia, abdominal pain, nausea and vomiting, bloody diarrhea, and shock. Later swelling of the salivary glands, stomatitis, loosening of the teeth, nephritis, anuria, and hepatitis occur. Death results from the effects of the gastrointestinal tract (ulcerations, bleeding, shock) and/or kidney (Carson et al., 1987).

H.1.11.6 Chronic Toxicity

The occupational exposure of workers to elemental mercury vapors (0.1 to 0.2 mg/m^3) has been associated with mental disturbances, tremors and gingivitis (EPA, 1984). The central nervous system is a major target for organic mercury compounds. Adverse effects in humans from exposure to organic mercury compounds have included the destruction of cortical cerebral neurons, damage to Purkinje cells and lesions of the cerebellum. Clinical symptoms following exposure to organic mercury compounds have included paresthesia, loss of sensation in extremities, ataxia, and hearing and visual impairment (WHO, 1976).

A primary target organ for inorganic mercurials is the kidney. Human exposure to inorganic mercury compounds has been associated with anuria, polyuria, proteinuria and renal lesions (Hammond and Beliles, 1980).

H.1.11.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Both organic and inorganic compounds are reported to be mutagenic in eukaryotic systems (Leonard et al., 1984).

Carcinogenicity

There is no definitive evidence reported in the literature indicating that either organic or inorganic mercury is carcinogenic by the ingestion, inhalation, or dermal pathways (ATSDR, 1989, Toxicological Profile for Mercury, PB90-181256). One positive study involving the ingestion pathway has been reported. Dietary exposure of mice to 15 ppm of methyl mercury in their diet resulted in renal tumors in 13 of 16 males, but in no females, surviving after 53 weeks. Eleven of the tumors in males were classified as adenocarcinomas and two as adenomas (EPA 1985).

Teratogenicity

Embryotoxic and teratogenic effects, including malformations of the skeletal and genitourinary systems, have been observed in the offspring of animals exposed to organic mercury (EPA, 1984).

H.1.11.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

Mercury is not classified as a human carcinogen (Group D), based on insufficient data in animals, and no human data.

EPA Dose-Response Parameters

No carcinogenic or noncarcinogenic dose-response parameters are reported in IRIS for Mercury. HEAST (1993) reports an oral chronic and subchronic RfD of 3.0E-04 mg/kg/day, and an inhalation chronic and subchronic RfC of 3.0E-04 mg/cm^3.

H.1.11.9 References

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H.1.12 Methylene chloride

H.1.12.1 Background

Methylene chloride (dichloromethane; DCM) is a multipurpose solvent used in industry for a variety of purposes including paint removal, manufacture of photographic equipment, as an aerosol propellant, in the manufacture of insecticides and fumigants, and as solvents and cleaners (Proctor and others, 1988). Methylene chloride is also produced in chlorinated drinking water treatment (NAS, 1977). DCM is a volatile liquid with high lipid (fat) solubility and moderate water solubility. Background ambient air concentrations of methylene chloride in the United States generally fall between 30 to 50 ppt (parts per trillion) (Brodzinsky and Singh, 1983; ATSDR, 1987), while the highest ambient air levels were measured in New Jersey at 360 ppb (Pellizzari and Bunch, 1979). Concentrations in drinking water average around 1 µg/l up to a maximum of 3 µg/l (U.S. Environmental Protection Agency, 1985).

DCM is readily absorbed from the respiratory and gastrointestinal tracts and more slowly across the skin (ATSDR, 1987). Due to the volatile nature of DCM, the principal route of exposure for humans is via inhalation. The absorption efficiency following inhalation is estimated to be 70 to 75 percent (DiVincenzo and Kaplan, 1981). It does tend to bioaccumulate, but the uptake is saturable, with establishment of a steady-state condition where intake and elimination are equal (ATSDR, 1987). Elimination from the body occurs primarily through exhaled air as unchanged DCM, carbon dioxide or carbon monoxide (ATSDR, 1987).

H.1.12.2 Acute Toxicity

Acute exposures to high concentrations of methylene chloride via oral and inhalation routes can cause severe toxic effects to a variety of organs. The principal target organs of DCM exposure are the liver and central nervous system (CNS). Impaired CNS function in humans from acute exposures to DCM (300-800 ppm for 5 hours) produced visual and auditory dysfunctions and decreased ability in various psychomotor tasks (Fodor and Winneke, 1971). Several cases of accidental human fatalities have occurred from acute exposures to high concentrations of methylene chloride (Bonventre and others, 1977). In animal studies, liver toxicity was evident following high doses of DCM (>4,000 ppm). Specific liver alterations included fatty infiltration,

glycogen depletion, altered cytochrome P-450 activity, and increased liver weights (ATSDR, 1987). In addition, kidney damage and cardiovascular effects have also been observed in animals following acute exposures.

H.1.12.3 Chronic Toxicity

As in acute exposures, the central nervous system, the cardiovascular system, and the liver are the principal target organs affected. Animal studies have shown an aging effect in liver cells, fatty proliferation in the liver, and altered liver enzyme levels (ATSDR, 1987). However, liver toxicity has not been reported in human epidemiological studies. The greatest effect of chronic exposure in humans appears to be on the cardiovascular and the central nervous system (ATSDR, 1987). Cardiovascular symptoms of chronic DCM exposure include chest pain (burning sensations around the heart), feelings of chest pressure and palpitations (ATSDR, 1987). Neurotoxic symptoms following DCM exposure include impaired short-term memory, insomnia, narcosis, and auditory and visual hallucinations (Weiss, 1967; NIOSH, 1976). Other organs suspected to be affected include the kidney and respiratory tract, but evidence is lacking to confirm the occurrence of these effects in humans (ATSDR, 1987).

H.1.12.4 Carcinogenicity

Two human epidemiological studies have been conducted on the carcinogenicity of methylene chloride. Friedlander and others (1978) examined the proportionate mortality of 344 workers exposed to air concentrations of DCM ranging between 30 and 125 ppm (time-weighted average) for up to 30 years. No significant increase in the cancer mortality rate of the exposed populations were observed relative to an unexposed control population. In another study of workers exposed to 26 ppm DCM for 22 years, no significant excess deaths from malignant neoplasms, respiratory cancer, or liver cancer were detected (Hearne and others, 1987; ATSDR, 1987). However, there was an increased incidence of deaths due to pancreatic cancer, although this was not statistically significant.

There is sufficient evidence that methylene chloride is carcinogenic in several animal species. In a two-year study conducted by the National Coffee Association (NCA, 1982 and 1983), rats

and mice were administered up to 250 mg/kg DCM in drinking water. Female rats and male mice exhibited a statistically significant increase in the incidence of neoplastic nodules or hepatocellular (liver) carcinomas, while these measures were not significant in female mice and male rats (U.S. Environmental Protection Agency, 1989). Burek and others (1980 and 1984) reported an increased incidence of mammary and salivary gland tumors in both male and female rats exposed to high concentrations of DCM. In another study, rats exposed to airborne DCM (up to 4,000 ppm) had an increased incidence of mammary adenomas, while male mice were found to have an excess of hepatocellular (liver) and respiratory adenomas and carcinomas (NTP, 1986). The USEPA has reviewed the available carcinogenicity data and has categorized methylene chloride as a probable human carcinogen (Group B2) based on inadequate data in humans and sufficient evidence of carcinogenicity in animals (U.S. Environmental Protection Agency, 1991).

H.1.12.5 Mutagenicity

DCM has been shown to be mutagenic in the Ames assay (with and without metabolic activation) (ATSDR, 1987). DCM was positive at inducing chromosomal aberrations in mouse and human lymphocytes (Thilagar and others, 1984). Generally negative results have been obtained for sister chromatid exchange, point mutation, and DNA damage and repair in cultured mammalian cells (ATSDR, 1987).

H.1.12.6 Reproductive/Developmental Effects

No studies are available on the reproductive or developmental effects of DCM in exposed humans. Two animal studies were conducted on reproductive effects of DCM; both studies reported negative results (Nitschke and others, 1985; Bornmann and Loesser, 1967). There is limited animal data available which indicates that DCM is a developmental toxin when inhaled at high concentrations (1,250 ppm) (ATSDR, 1987). The significance of these results is not clear, however, since the reported effects were not significantly different from controls, the studies used only one dose, and the exposure concentrations caused maternal toxicity (which in turn may have caused fetal toxicity) (ATSDR, 1987).

H.1.12.7 Sensitive Populations

Approximately 1 million workers employed in industries such as DCM manufacturing, paint remover formulation, and metal degreasing are at an elevated risk compared to the general population (ATSDR, 1987). Additionally, individuals living near industries producing or utilizing DCM in large quantities are at risk of occasional atmospheric exposure. Individuals with a weakened cardiovascular system may be more sensitive to DCM exposure since low levels of DCM may enhance the severity of existing cardiovascular disease (ATSDR, 1987).

H.1.12.8 Chemical Interactions

No information is available on potential interactions with other chemicals.

H.1.12.9 Dose-Response Parameter Estimates

The dose-response parameter estimates for carcinogens and noncarcinogens are computed differently by USEPA; therefore, these estimates are presented separately below.

Carcinogenic Effects:

The Cancer Assessment Group (CAG) of the USEPA has derived an oral cancer potency estimate of 7.5×10^{-3} $(mg/kg/day)^{-1}$ (U.S. Environmental Protection Agency, 1991a). This estimate is based on the arithmetic mean of the potency slope factors determined for hepatocellular adenomas and carcinomas in mice from lifetime inhalation exposure studies conducted by the National Toxicology Program (NTP, 1986) and the National Coffee Association (NCA, 1983), as discussed above. The CAG has also derived an inhalation cancer potency estimate of 1.4×10^{-2} $(mg/kg/day)^{-1}$ based on the combined incidence of adenomas and carcinomas of the liver or lung from the NTP study (NTP, 1986).

Oral Cancer Potency Estimates: 7.5×10^{-3} $(mg/kg/day)^{-1}$

(U.S. Environmental Protection Agency, 1991a).

Inhalation Cancer Potency Estimate: 1.4×10^{-2} $(mg/kg/day)^{-1}$

(U.S. Environmental Protection Agency, 1991a).

Noncarcinogenic Effects:

The USEPA has computed a chronic oral reference dose (RfD) of 6 x 10^{-2} mg/kg/day for methylene chloride (U.S. Environmental Protection Agency, 1991a) based on a two-year drinking water study with rats, which identified a NOAEL (no-observed-adverse-effect-level) of 6 mg/kg/day (NCA, 1982). Higher doses produced histological alterations of the liver. An uncertainty factor of 100 was incorporated to account for uncertainties in extrapolating animal data to humans (10) and to account for sensitive human subgroups (10) (U.S. Environmental Protection Agency, 1991a). An inhalation RfD of 3 mg/m^3 (U.S. Environmental Protection Agency, 1991b) was derived for methylene chloride by the USEPA.

Oral RfD: 6 x 10^{-2} mg/kg/day (U.S. Environmental Protection Agency, 1991a).

Inhalation RfD: 3 mg/m^3 (U.S. Environmental Protection Agency, 1991b).

H.1.12.10 References

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H.1.13 Nickel

H.1.13.1 Occurrence and Use

Nickel (Ni) is a naturally occurring metal in the earth's crust and known to exist in at least 4 valence states. The water soluble nickel salts (+2 state) are the most common form, while other nickel compounds include nickel carbonyl, nickel subsulfide and nickel dust. Typical levels of nickel in soils range from approximately 6 to 60 ppm (Kabata-Pendias and Pendias, 1987).

Nickel (Ni) is an important element used for electroplating coatings for turbine blades, helicopter rotors, extrusion dyes, coinage, ceramics, storage vessels, batteries, and electronic circuits as well and as in the production of steel and many other alloys.

H.1.13.2 Physical and Chemical Properties of Nickel

Molecular Weight	59.00[1]
Water Solubility, mg/l	0.0E+00[2]
Vapor Pressure, mm Hg	0.0E+00[3]
Bioaccumulation Factor for Fish	1.0E+02[4]
Bioaccumulation Factor for Shellfish	1.0E+02[4]

Sources: [1]Multi-Media Exposure Assessment Manual, 1989
[2]Weast, 1979
[3]Callahan et al., 1979
[4]Napier et al., 1980

H.1.13.3 Routes of Exposure, Absorption, Distribution, Transport, and Degradation

The major source of human exposure is in the workplace by inhalation of dust and fumes and skin contact, but it can also affect the general populations by ingestion of contaminated food stuffs and drinking water, usually in the form of nickel salts.

Nickel compounds can be absorbed following inhalation, ingestion. Dermal absorption results in allergic reactions only at the sites of skin contact. The amount absorbed depends on the dose

administered and on the chemical and physical form of the particular nickel compound (EPA, 1986). The principal tissues and organs to which nickel and its compounds are distributed have been reported to include kidneys, pituitary glands, lings, skin, adrenal glands, ovaries, and testes. Major routes of excretion have been studied in rats, which indicate that the principal route of elimination is the urine. Other routes of excretion include the bile, sweat, hair and mother's milk (ATSDR, 1989).

H.1.13.4 Acute Toxicity

Noncarcinogenic effects of nickel exposure include nausea, fever, lung inflammation and respiratory failure following acute incidences, as well as contact dermatitis (skin rashes). Adverse effects associated with acute exposure in animals have included depressed weight gain, altered hematological parameters, and increased iron deposition in the blood, heart, liver and testes (EPA, 1987).

H.1.13.5 Chronic Toxicity

Chronic ingestion of nickel-containing foods increases the risk of developing skin rashes. Studies performed in animals to estimate the long-term effects of nickel exposure showed a decrease in body and organ weights of rats (may be indicative of disease), as well as a decrease in their appetite.

Chronic or subchronic exposures of experimental animals to nickel salts have been associated with reduced weight gain, degenerative lesions of the male reproductive tract, asthma, nasal septal perforations, rhinitis, sinusitis, hyperglycemia, decreased prolactin levels, decreased iodine uptake, and vasoconstriction of the coronary vessels (Clayton and Clayton, 1981).

H.1.13.6 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Results of mutagenicity assays suggest that nickel is mutagenic. Nickel carbonate caused DNA strand breaks, and reduced the fidelity of DNA replication. In mammalian cells, nickel chloride produced mutations in Chinese hamster V79 and ovary cells, as well as in mouse lymphoma

cells. At least ten investigations of nickel causation of chromosomal aberrations have been conducted, with four positive results in cells of mice, hamsters, and humans, and six negative studies in cells of humans, mice and rats (ATSDR, 1989).

Carcinogenicity

It has been known for over 40 years that inhalation of nickel is associated with the development of lung, nasal and respiratory cancer. However, an evaluation of the carcinogenicity soluble salts of nickel, which are possible contaminants of soil, water, food, has not been performed.

Inhalation exposure of experimental animals to nickel carbonyl or nickel subsulfide induces pulmonary tumors (EPA, 1986). Several nickel salts cause localized tumors when administered by subcutaneous injection or implantation. Epidemiological evidence indicates that inhalation of nickel refinery dust and nickel subsulfide is associated with cancers of the nasal cavity, lung, larynx, kidney and prostate (EPA, 1986).

Teratogenicity

Nickel can cross the placental barrier, but there is no definitive evidence of teratogenicity. Nickel carbonyl was teratogenic in rats; i.v. doses of $NiCl_2$ (1 to 6.9 mg/kg) on single days 7 through 11 was teratogenic in mice (Carson et al., 1987).

H.1.13.7 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

Nickel refinery dust and nickel subsulfide (the compound used in this risk assessment) for conservatism by inhalation are both categorized in Group A - Human Carcinogens.

EPA Dose-Response Parameters (IRIS, 1994)

Oral RfD Summary :

ORAL RfD : 0.02 mg/kg/day

CRITICAL EFFECT : Decreased body and organ weights in rats

ORAL RfD UNCERTAINTY

UF = 300. An uncertainty factor of 10 is used for interspecies extrapolation and 10 to protect sensitive populations. An additional uncertainty factor of 3 is used to account for inadequacies in the reproductive studies (RTI, 1987; Ambrose et al., 1976; Smith et al., 1990) (see Additional Comments section). During the gestation and postnatal development of F1b litters in the RTI (1987) study, temperatures were about 10 degrees F higher than normal at certain times, which makes evaluation of this part of the reproductive study impossible. In the Ambrose et al. (1976) study, statistical design limitations included small sample size and use of pups rather than litters as the unit for comparison. There were also problems with the statistical analysis of the Smith et al. (1990) study.

ORAL RfD MODIFYING FACTOR

MF = 1.

ORAL RfD CONFIDENCE :

Study: Low

Data Base: Medium

RfD: Medium

The chronic study (Ambrose et al., 1976) was properly designed and provided adequate toxicological endpoints; however, high mortality occurred in the controls (44/50). Therefore, a low confidence is recommended for the study. The data base provided adequate supporting subchronic studies, one by gavage and the other in drinking water (Po animals of the RTI subchronic study, 1986). A medium confidence level in the data base is recommended since there are inadequacies in the remaining reproduction data.

INHALATION RfD SUMMARY

No inhalation RfD is available for nickel from IRIS (1994).

H.1.13.8 References

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H.1.14 Silver

H.1.14.1 Occurrence and Use

Silver occurs naturally as a free metal, but is most widely distributed as an alloy in the forms of Ag_2S (argentite), AgCl (cerargerite), and as Ag_3As (silver arsenide). Silver is often found as an impurity in the ores of zinc, copper, and lead. It also exists in combination with sulfides of copper, arsenic, and antimony. Almost all soils, sea water and some fresh waters contain traces of silver (Petering and McClain 1991). Typical levels of silver in natural soils range from 0.04 to 1.0 mg/kg (Kabata-Pendias and Pendias, 1986).

Major uses of silver include electroplated ware, sterling ware, photographic materials, brazing alloys and solder, and electrical contacts and conductors. Minor uses include jewelry, dental and medical supplies, batteries, catalysts, and bearings (Carson et al., 1987). The toxicity of silver compounds is generally considered to be moderate, although large doses of silver compounds may have serious effects (EPA 1980).

H.1.14.2 Physical and Chemical Properties of Silver

Molecular Weight	108.00
Water Solubility, mg/l	0.0E+00
Vapor Pressure, mm Hg	0.0E+00
Bioaccumulation Factor for Fish	2.3E+00
Bioaccumulation Factor for Shellfish	7.7E+02

Source: Multi-Media Exposure Assessment Manual, 1989

H.1.14.3 Environmental Fate and Transport

Silver resulting from anthropogenic activities is widely distributed in the environment. Its occurrence in rain water may permit transport to remote places in the ecosystem. This source could account for the finding of silver in many sewage sludges in measurable amounts. Sludges in the USA have been found to be high enough in silver to increase the silver in sludge-amended soils ten-fold. Silver is present in plants in the range of 0.06 to 0.28 µg/g dry weight. In fungi

and bacteria silver is present in amount of about 29 to 210 µg/g respectively. Aquatic plants tend to concentrate silver form their environments several hundred-fold (Petering and McClain, 1991).

H.1.14.4 Routes of Exposure, Absorption, Distribution, Transport, and Degradation

Silver may enter the body via the respiratory tract, the gastrointestinal tract, mucous or broken skin and possibly by absorption through intact skin. Up to 10% of a single oral dose of silver is absorbed. Absorption from nonintact skin is believed less than 1%. The amount of silver administered, its chemical form, and the route by which it is administered affect the tissue content and distribution of silver within the body (Furchner et al., 1968). It is retained by all body tissues. The primary sites of deposition in persons never having taken silver for therapeutic reasons are the liver, skin, lungs, adrenals, muscle, pancreas, kidney, heart and spleen. Silver is also deposited in blood vessel walls, testes, pituitary, nasal mucous membrane, maxillary antra, trachea and bronchi (Sax, 1963).

H.1.14.5 Acute Toxicity

Acute toxic effects associated with silver compounds can occur in humans under unusual, and unusually intense, exposure scenarios, such as in intentional or accidental poisoning, which differs qualitatively and quantitatively from environmental exposure scenarios. Large acute doses of silver salts in humans attempting suicide have produced severe abdominal pain, rigidity, vomiting, convulsions, and shock. Autopsies of fatal attempts have revealed pulmonary edema, hemorrhage, and necrosis of the bone marrow, liver, and kidney. Pulmonary edema was observed in animals administered intravenous injections of 32 mg/kg silver nitrate (ATSDR, 1989).

H.1.14.6 Chronic Toxicity

Generalized argyria, localized argyria and argyrosis (argyria of the eye) are the most common effects of chronic and less frequently subacute human exposure to silver or silver compounds. Generalized argyria is characterized by a slate gray pigmentation of the skin, hair, and internal organs and used by deposition of silver in the tissues (Goyer, 1986).

H.1.14.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Silver compounds have been reported to be non-mutagenic in a variety of bacterial test systems, for example, in Escherichia coli, Salmonella typhimurium, and Bacillus subtilis (ATSDR, 1989).

Carcinogenicity

There is insufficient evidence that silver is carcinogenic to either humans or animals (ATSDR, 1989).

Teratogenicity

There is no evidence available in the literature to indicate whether or not silver or silver compounds may exert adverse developmental effects.

H.1.14.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

Silver is not classifiable as to human carcinogenicity (Group D), Based on insufficient data. In animals, local sarcomas have been induced after implantation of foils and discs of silver. However, the interpretation of these findings has been questioned due to the phenomenon of solid-state carcinogenesis in which even insoluble solids such as plastic have been shown to result in local fibrosarcomas.

EPA Dose-Response Parameters

Carcinogenic Effects:

No dose-response parameters have been promulgated for carcinogenic response to cadmium.

Noncarcinogenic Effects:

ORAL RfD SUMMARY:

RfD : 5E-3 mg/kg/day

CRITICAL EFFECT/TARGET ORGAN: Argyia in humans following chronic exposure.

ORAL RfD UNCERTAINTY :

UF = 3. An uncertainty factor of 3 is applied to account for minimal effects in a subpopulation which has exhibited an increased propensity for the development of argyria. The critical effect observed is a cosmetic effect, with no associated adverse health effects. Also, the critical study reports on only 1 individual who developed argyria following an i.v. dose of 1 g silver (4 g silver arsphenamine). Other individuals did not respond until levels five times higher were administered. No uncertainty factor for less than chronic to chronic duration is needed because the dose has been apportioned over a lifetime of 70 years.

ORAL RfD MODIFYING FACTOR :

MF = 1.

ORAL RfD CONFIDENCE:

Study: Medium

Data Base: Low

RfD: Low

The critical human study rates a medium confidence. It is an old study (1935) which offers fairly specific information regarding the total dose of silver injected over a stated period of time. One shortcoming of the study is that only patients developing argyria are described; no information is presented on patients who received multiple injections of silver arsphenamine without developing argyria. Therefore, it is difficult to establish a NOAEL. Also, the individuals in the study were being treated for syphilis and may have been of compromised health.

Confidence in the data base is considered to be low because the studies used to support the RfD were not controlled studies. For clinical case studies of argyria (such as Blumberg and Carey, 1934; East et al., 1980), it is especially difficult to determine the amount of silver that was ingested.

Confidence in the RfD can be considered low-to-medium because, while the critical effect has been demonstrated in humans following oral administration of silver, the quantitative risk estimate is based on a study utilizing intravenous administration and thus necessitates a dose conversion with inherent uncertainties.

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H.1.15 Tetrachloroethene

H.1.15.1 Occurrence and Use

Tetrachloroethene (also referred to as perchloroethylene; PCE) is an organic chemical widely used as a solvent, predominantly in the dry-cleaning industry. It is also used in the manufacture of textiles, as a constituent of rubber, paint removers, inks and cleaning fluids (Fawell and Hunt, 1988). Tetrachloroethene (PCE) is not known to occur naturally in the environment but is commonly detected in urban air. For example, reported levels of PCE in New York City have ranged between 0.1 and 8.7 mg/m^3 (Lillian and others, 1975), while air concentrations in rural areas are much lower.

H.1.15.2 Physical/Chemical Properties of Tetrachloroethene

Molecular Weight	165.85[1]
Water Solubility, mg/l	1.5E+02[2]
Vapor Pressure, mm Hg	1.8E+01[2]
Henry's Law Constant, atm-m^3/mole	2.6E-02[3]
Octanol-Water Partition Coefficient	4.0E+02[2]
Organic Carbon Partition Coefficient (L/g)	3.6E+02[4]
Bioaccumulation Factor for Fish	5.6E+01[1]
Bioaccumulation Factor for Shellfish	9.6E+00[1]

Sources: [1]Multi-Media Exposure Assessment Manual, 1989
[2]U.S. Environmental Protection Agency, 1984
[3]ICF-Clement Associates, 1987
[4]Mabey and others, 1982

H.1.15.3 Environmental Fate and Transport

Tetrachloroethene (PCE) is likely to enter the environment by fugitive air emissions from dry cleaning and metal degreasing industries and by spills or accidental releases to air, soil, or water. If PCE is released to soil, it will be subject to evaporation into the atmosphere and to leaching to the groundwater. Biodegradation may be an important process in anaerobic soils based on

laboratory tests with methanogenic columns. Slow biodegradation may occur in groundwater where acclimated populations of microorganisms exist. If PCE is released to water, it will be subject to rapid volatilization with estimated half-lives ranging from <1 day to several weeks. It will not be expected to significantly biodegrade, bioconcentrate in aquatic organisms or significantly adsorb to sediment. PCE will not be expected to significantly hydrolyze in soil or water under normal environmental conditions. If PCE is released to the atmosphere, it will exist mainly in the gas-phase and it will be subject to photooxidation with estimates of degradation time scales ranging from an approximate half-life of 2 months to complete degradation in an hour. Some of the PCE in the atmosphere may be subject to washout in rain based on the solubility of PCE in water; PCE has been detected in rain (Hazardous Substance Database, 1993).

H.1.15.4 Pharmacokinetics (Routes of Exposure, Distribution, Absorption, Transport)

Major human exposure is from inhalation of contaminated urban air, especially near point sources such as dry cleaners, drinking contaminated water from contaminated aquifers and drinking water distributed in pipelines with vinyl liners, and inhalation of contaminated occupational atmospheres in metal degreasing and dry cleaning industries (Hazardous Substance Database, 1993).

The principal route of human exposure is through inhalation of airborne tetrachloroethylene (PCE). The efficiency of pulmonary absorption is a function of ventilation rate, duration of exposure, atmospheric concentration and individual total body fat (Agency for Toxic Substances and Disease Registry, 1987). Generally, PCE is initially readily absorbed from the respiratory tract (approximately 100 percent) of humans, but long exposure duration results in a decrease in absorption efficiency (absorption decreased to 60 percent of its initial value after 4 hours of exposure) (Agency for Toxic Substances and Disease Registry, 1987). PCE is absorbed from the gastrointestinal (GI) tract of humans, although apparently not completely (no quantitative estimates were available) (Fawell and Hunt, 1988). In experimental studies using rats and mice, GI absorption was rapid and complete (Agency for Toxic Substances and Disease Registry, 1987). In experimental animals, the majority of an inhaled or ingested dose of PCE (>70 percent) is eliminated unchanged in exhaled air (Fawell and Hunt, 1988). The remainder is principally distributed to adipose tissue. Exposed human volunteers exhaled between 38 and 100

percent of the dose unchanged depending on the study (Fawell and Hunt, 1988). In addition, a small amount (2%) of PCE is metabolized in the liver to its epoxide intermediate by the mixed function oxidase system (Fawell and Hunt, 1988).

H.1.15.5 Acute Toxicity

The predominant effect in exposed humans is central nervous system (CNS) depression, with symptoms ranging from lightheadedness and loss of coordination to unconsciousness and respiratory paralysis (Steward, 1969). Typically, however, respiratory irritation, headache, dizziness, and drowsiness are common symptoms reported in acute human exposures. Although the data is not clear, the threshold for human neurotoxic effects appears to be somewhere between 100 to 200 ppm (Agency for Toxic Substances and Disease Registry, 1987). Other observed effects of acute PCE exposures include burning and lacrimation of the eyes, hepatotoxicity, cardiac and immunologic toxicity (Agency for Toxic Substances and Disease Registry, 1987). Human cases of hepatotoxic effects have originated almost exclusively from accidental exposures, where exposures were not quantified but believed to be quite high. Hepatotoxic effects include cirrhosis, toxic hepatitis, necrosis, and altered liver enzyme function (Agency for Toxic Substances and Disease Registry, 1987). PCE is not extremely toxic by the oral route and actually was prescribed to humans at doses of 0.1 ml/kg up to 5 ml/kg for anthelminthic purposes (Fawell and Hunt, 1988). Further, a dose of 500 mg/kg was not lethal when administered to patients (Torkelson and Rowe, 1982). The oral LD_{50} in rats was 2.6 g/kg (Torkelson and Rowe, 1982).

H.1.15.6 Chronic Toxicity

The target organs of chronic exposures to PCE are the CNS and the liver. Occupationally exposed workers at dry-cleaners report toxic symptoms of dizziness, drowsiness, and irritation to the eyes, nose and throat (Fawell and Hunt, 1988). No CNS effects were noted in humans at PCE levels of 20 ppm, while 100 ppm elicited a decrease in coordination skills (Hake and Stewart, 1977). Individuals chronically exposed to PCE develop a tolerance to the CNS and irritant properties of PCE. Buben and O'Flaherty (Buben and O'Flaherty, 1985) administered tetrachloroethylene orally to mice at doses ranging from 20 to 2000 mg/kg/day, 5 days/week for

6 weeks and then evaluated four liver function criteria: liver weight, triglyceride levels, glucose-6-phosphate (G6P) activity, and serum glutamate pyruvate transaminase (SGPT) levels. No effects were observed at 20 mg/kg while liver weight and triglyceride levels were significantly increased at doses greater than 100 mg/kg. G6P was significantly decreased and SPGT was significantly increased at doses greater than 500 mg/kg (Buben and O'Flaherty, 1985).

H.1.15.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Nearly all studies indicate no mutagenic effects of tetrachloroethylene. Negative results have been reported, both with and without metabolic activation, in the Ames assay using Salmonella typhimurium (Bartsch and others, 1979). PCE was nonmutagenic in E. coli, both with and without activation (Greim and others, 1975). In addition, PCE did not cause mitotic gene conversions, mitotic crossing over or reverse mutations in Saccharomyces cerevisiae or chromosomal aberrations in mice and rat bone marrow cells in vivo (Fawell and Hunt, 1988). In contrast, one report is available showing mutagenic effects in a host-mediated assay in bacteria and mouse bone marrow cells (Cerna and Kypenova, 1977).

Carcinogenicity

The data on human carcinogenicity is not clear. Studies of cancers in dry-cleaning and laundry workers indicate small increases in cancers of the lung, cervix, skin, bladder and kidneys in exposed workers (Fawell and Hunt, 1988). However, these workers were also exposed to a variety of other solvents, which make interpretation of the data difficult. Experimental studies using laboratory animals also have produced contrasting results. Nevertheless, in an inhalation study, an increased incidence of leukemia was seen in rats exposed to 200 or 400 ppm and liver tumors in mice exposed to 100 or 200 ppm tetrachloroethylene for 2 years were reported (National Toxicology Program, 1986). In an oral study, rats and mice were administered 500 or 1000 mg/kg PCE, 5 days/week for 78 weeks resulting in a significant increase in hepatocellular carcinomas in treated animals without any effects on other organs (NCI, 1977). The USEPA has categorized PCE as a probable human carcinogen (Group B_2) based on a weight-of-evidence scheme (U.S. Environmental Protection Agency, 1990).

Teratogenicity (and other reproductive effects)

There is no information available on reproductive or developmental effects of PCE in humans. Mice exposed to 500 ppm PCE 8 hours/day, 5 days/week experienced a slight increase in the frequency of abnormal sperm after 4 weeks of exposure (Agency for Toxic Substances and Disease Registry, 1987). Pregnant rats and mice exposed to 300 ppm PCE for 7 hours/day on gestational days 6 to 15, delivered offspring with reduced mean weights, reduced liver weights, and increased subcutaneous edema (Schwetz and others, 1975). Teratogenic effects or major developmental disturbances were not noted. A high concentration of trichloroacetic acid (a metabolite of tetrachloroethylene) was observed in the amniotic fluid of fetuses of exposed dam, thus indicating rapid transplacental migration and potential long-term fetal exposure (Agency for Toxic Substances and Disease Registry, 1987).

H.1.15.8 USEPA Carcinogenic Classification and USEPA Dose-Response Parameters

USEPA Carcinogenic Classification

In USEPA's issue papers from the Environmental Criteria and Assessment Office (ECAO), Superfund Health Risk Technical Support Center (U.S. Environmental Protection Agency, 1993), tetrachloroethane is classified in the C-B2 continuum. The oral slope factor and inhalation unit risk values are cited as 0.052 $(mg/kg/day)^{-1}$ and 5.8E-07 $(\mu g/m^3)^{-1}$.

USEPA Dose-Response Parameters

ORAL RfD : 1E-2 mg/kg/day

CRITICAL EFFECT/TARGET ORGAN : Hepatotoxicity, weight gain

ORAL RfD UNCERTAINTY : UF = 1000.

The uncertainty factor of 1000 results from multiplying factors of 10 to account for intraspecies variability, interspecies variability and extrapolation of a subchronic effect level to its chronic equivalent.

ORAL RfD MODIFYING FACTOR : MF = 1.

Oral RfD Confidence

Study: Low

Data Base: Medium

RfD: Medium

No one study combines the features desired for deriving an RfD: oral exposure, large number of animals, multiple dose groups, testing in both sexes and chronic exposure. Confidence in the principal studies is low mainly because of the lack of complete histopathological examination at the NOAEL in the mouse study. The data base is relatively complete but lacks studies of reproductive and teratology endpoints subsequent to oral exposure; thus, it receives a medium confidence rating. Medium confidence in the RfD follows.

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H.1.16 Toluene

H.1.16.1 Occurrence and Use

Toluene is a flammable aromatic hydrocarbon commercially produced by the petrochemical industry. It is used in the manufacture of dyes, saccharin, perfumes, caprolactam, pharmaceuticals, detergents and trinitrotoluene (TNT) (Fawell and Hunt, 1988). It is also used as a solvent and is a component in automobile and aviation fuel (Fawell and Hunt, 1988). Atmospheric concentrations of toluene have been linked with automobile exhaust emissions in a number of studies (Fawell and Hunt, 1988). Toluene has been identified in several surveys of raw and treated water in the U.S. at average concentrations of less than 1 mg/l (Fawell and Hunt, 1988). Levels in surface waters were generally less than 1 mg/l, but up to 5 mg/l were found in some groundwaters (Fawell and Hunt, 1988).

H.1.16.2 Physical and Chemical Properties of Toluene

Molecular Weight	92.15[1]
Water Solubility, mg/l	5.4E+02[2]
Vapor Pressure, mm Hg	2.8E+01[2]
Henry's Law Constant, atm-m^3/mole	6.4E-03[3]
Octanol-Water Partition Coefficient	5.4E+02[2]
Organic Carbon Partition Coefficient, L/g	3.0E+02[4]
Bioaccumulation Factor for Fish	7.0E+01[1]
Bioaccumulation Factor for Shellfish	1.2E+01[1]

Sources: [1] HSDB,1989
[2] USEPA, 1984
[3] ICF, 1987
[4] Mabey, et al., 1982

H.1.16.3 Environmental Fate and Transport

Toluene is released into the atmosphere principally from the volatilization of petroleum fuels and toluene-based solvents and thinners and from motor vehicle exhaust. Considerable amounts are

discharged into waterways or spilled on land during the storage,transport and disposal of fuels and oils. If toluene is released to soil, it will be lost by evaporation from near-surface soil and by leaching to the groundwater. Biodegradation occurs both in soil and groundwater, but it is apt to be slow especially at high concentrations, which may be toxic to microorganisms. The presence of acclimated microbial populations may allow rapid biodegradation. It will not significantly hydrolyze in soil or water under normal environmental conditions. If toluene is released into water, its concentration will decrease due to evaporation and biodegradation. This removal can be rapid or take several weeks, depending on temperature, mixing conditions, and acclimation of microorganisms. It will not significantly adsorb to sediment or bioconcentrate in aquatic organisms. If toluene is released to the atmosphere, it will degrade by reaction with photochemically produced hydroxyl radicals (half-life 3 hr to slightly over 1 day) or be washed out in rain. It will not be subject to direct photolysis (HSDB, 1993).

H.1.16.4 Pharmacokinetics (Routes of Exposure, Distribution, Absorption, Transport, and Degradation)

The primary source of human exposure is from inhalation of contaminated ambient air, especially in traffic or near filling stations, or in occupational atmospheres where toluene-based solvents are used (HSDB, 1993).

The most common route of exposure in humans is by inhalation. In human subjects, pulmonary absorption of toluene was 57 percent after exposure to 430 m/m^3 for one hour and declined to a steady-state level of 37 percent of the dose after 2-4 hours (Nomiyama and Nomiyama, 1974). Several factors are known to affect pulmonary absorption rates such as ventilatory rate, particle size, solubility and for organics, body fat. Animal studies indicate near complete (approximately 100 percent) absorption of toluene from the gastrointestinal tract (USEPA, 1985). Toluene is also absorbed across the skin. Once absorbed, toluene would be expected to distribute to lipid or adipose tissue due to its low solubility and lipophilicity. Studies in rats indicate rapid distribution with tissues reaching maximum levels within hours of dosing. Toluene was distributed in highest concentrations to the liver, brain and blood of mice in several studies (USEPA, 1989). Toluene is rapidly hydroxylated by the mixed function oxidase system to benzyl alcohol. Further

metabolism results in the formation of hippuric acid or the glucuronide conjugate of benzoic acid, both of which are eliminated in urine and account for 85-95 percent of an absorbed dose (hippuric acid accounts for 75 percent) (USEPA, 1985). Toluene is also eliminated unchanged in exhaled air. Elimination is rapid with no evidence of bioaccumulation seen in daily samples of occupationally exposed individuals (USEPA, 1985).

H.1.16.5 Acute Toxicity

Acute exposure to toluene results in central nervous system (CNS) depression and membrane irritation, though sudden deaths due to cardiac arrhythmias have been reported in some cases of toluene abuse (toluene and toluene-containing industrial solvents are often abused socially for the intoxication effect) (Fawell and Hunt, 1988). There is little evidence that toluene is acutely toxic to organs other than the CNS, although effects on the lungs, liver, and kidney have been reported following acute inhalation exposures (USEPA, 1989). However, toluene is not considered to be very toxic. The oral LD_{50} in rats is 7.0 g/kg (Fawell and Hunt, 1988).

H.1.16.6 Chronic Toxicity

Occupational exposures at concentrations of 300 ppm have resulted in CNS abnormalities (Fawell and Hunt, 1988). For example, exposed female shoemakers showed abnormal tendon reflexes, reduced grasping power, and decreased finger agility, while car painters showed impairment of concentration, reduced emotional reactivity and reduced hand agility (Fawell and Hunt, 1988). Studies of habitual "glue sniffers" abusing toluene-containing glues have reported symptoms consistent with those of occupationally exposed subjects and experimental animals. Associated neurological disorders include cerebellar degeneration, encephalopathy (brain degeneration), personality changes, slurred speech, clumsiness, and memory and concentration disturbances (Fawell and Hunt, 1988). Results of animal studies show no organ damage after exposure to very high doses of toluene (Fawell and Hunt, 1988). Rodents exposed to 12,000 ppm of toluene in 3 hour cycles 5 times per week for 8 weeks exhibited inebriation but no lung, liver, or kidney damage (Fawell and Hunt, 1988). In a two-year study of rats exposed to 30, 100, or 300 ppm of toluene, a dose-related reduction in hematocrit values (packed cell volume) was observed in females, but not males (USEPA, 1989a). No other effects were observed.

H.1.16.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

Chromosomal studies of toluene-exposed workers have produced equivocal results for mutagenicity. Workers exposed to toluene for up to 15 years displayed no significant increase in lymphocyte chromosomal aberrations (Fawell and Hunt, 1988). However, a study of workers in chemical laboratories and a photoprinting factory did indicate a significant increase in the frequency of abnormal lymphocytes and chromosome breaks (Fawell and Hunt, 1988). Toluene has been found to be nonmutagenic in reverse mutation assays with S. typhimurium and other mutagenic assays.

Carcinogenicity

Since human exposure in the workplace occurs often and because toluene is an abused substance, many reports on human exposure exist in the literature. None of these reports, however, associates toluene exposure with an increased rate or incidence of cancer. Likewise, carcinogenicity due to toluene exposure has not been observed in animal studies (USEPA, 1984).

No significant increases in tumor incidence was found in a two-year inhalation study of 120 rats exposed to 0, 30, 100, or 300 ppm of toluene for 6 hours per day, 5 days per week (Fawell and Hunt, 1988). Also, toluene applied to the skin of mice 3 times per week for a lifetime produced no carcinogenic effects (Fawell and Hunt, 1988). Toluene has not been tested for carcinogenicity by the oral route (Fawell and Hunt, 1988). Based on inadequate evidence in animals and lack of human data, the Carcinogen Assessment Group of the EPA has designated toluene as a Group D carcinogen (not classifiable as to human carcinogenicity) (USEPA, 1993).

Teratogenicity (and other reproductive effects)

Increased embryonic mortality was apparent in mice administered toluene by gavage on days 6-15 of gestation at doses of 0.3, 0.5 or 1.0 ml/kg (Fawell and Hunt, 1988). Also, decreased fetal weight was also noted at 0.5 and 1.0 ml/kg, and a significantly increased incidence of cleft palate was found at the highest dose.

H.1.16.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

There is insufficient evidence to classify toluene as a carcinogen. It is currently classified by the EPA as a Group D carcinogen (not classified) (USEPA, 1993).

EPA Dose-Response Parameters

INHALATION RfD: 1.1E-1 mg/kg/day

INHALATION RfC: 4E-1 mg/cu.m

CRITICAL EFFECT/TARGET ORGAN : Neurological effects , degeneration of nasal epithelium

INHALATION RfD UNCERTAINTY

UF = 300. An uncertainty factor of 10 is used to account for intraspecies variability and another factor of 10 for the use of a LOAEL. An additional factor of 3 is applied for data base deficiencies, including the lack of data and well-characterized laboratory animal exposures evaluating neurotoxicity and respiratory irritation.

Inhalation RfD Modifying Factor: MF -- None (=1)

INHALATION RfD CONFIDENCE

Study -- Medium

Data Base -- Medium

RfC -- Medium

The study of Foo et al. (1990) indicates adverse neurological effects of toluene in a small worker population. These effects are consistent with more severe CNS effects occurring at abusive concentrations of toluene and could not have been confounded by alcohol as the control and exposed populations did not use alcohol. However, the paucity of exposure information and identification of only a LOAEL is not sufficient to warrant a higher confidence than medium for this study. Other studies indicate that irritation may occur at around the same concentration, 100

ppm (Baelum et al., 1985; Echeverria et al., 1989). In regard to this effect, the NTP (1989) rat chronic inhalation study was well conducted, established the rat as the most sensitive species, examined an adequate number of animals, and performed histopathology on all major organs, including the brain and the respiratory tract. The sensitive endpoint was the concentration-dependent degeneration of the nasal epithelium characterized by the erosion of the olfactory epithelium and degeneration of the respiratory epithelium in male rats. The NTP study is also given medium confidence, however, as it did not establish a NOAEL. Although this data base has a complement of chronic laboratory animal studies, long-term data in humans are not available for either the neurotoxicity or irritation endpoints. The reproductive/developmental studies in three species were not comprehensive in endpoint evaluation but do identify the rabbit as the most sensitive species. The data base is thus given a medium confidence rating. A medium confidence rating for the RfC follows.

H.1.16.9 References

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H.1.17 Trichloroethene

H.1.17.1 Occurrence and Use

Trichloroethene (TCE) is a volatile organic hydrocarbon that is widely used as a solvent, degreasing agent, as an extracting of caffeine in coffee, and as a dry cleaning agent (Sittig, 1985). TCE is also used as a chemical intermediate in the manufacture of pesticides, waxes, tars, paints, chemicals. It was also used in the past as an anesthetic agent. While TCE is not produced naturally, it is a common environmental contaminant frequently detected in air, food and water. Mean atmospheric TCE levels in the United States have been reported at 30 ppt in remote areas, 460 ppt in urban areas and 1200 ppt in areas near emission sources (Brodzinsky and Singh, 1982). Analysis of an EPA database indicates that TCE was positively identified in 6 percent of the sampling stations in the U.S. with median levels below 5 ppb (ATSDR, 1988). Ingestion and inhalation are the primary routes of exposures, but TCE is also absorbed from skin and eyes (Sittig, 1985).

H.1.17.2 Physical and Chemical Properties of Trichloroethene

Molecular Weight	131.29[1]
Water Solubility, mg/l	1.1E+03[2]
Vapor Pressure, mm Hg	5.8E+01[2]
Henry's Law Constant, atm-m^3/mole	9.1E-03[3]
Octanol-Water Partition Coefficient	2.4E+02[2]
Bioaccumulation Factor for Fish	3.8E+01[1]
Bioaccumulation Factor for Shellfish	6.4E+00[1]

Sources: [1]Multi-Media Exposure Assessment Manual, 1989
[2]EPA, 1984
[3]ICF, 1987

H.1.17.3 Environmental Fate and Transport

Over 155 million pounds of trichlorethylene are used for vapor degreasing of metals(1) which should result in releases to the environment through evaporation, spills, and leaks in storage

tanks. Once in the environment, it is primarily removed by photooxidation in the atmosphere (atmospheric residence time - 5 days). Releases to water will primarily be removed by evaporation. Releases to soil will be partially evaporated and partially leached into groundwater, where it may remain for a long time. However, there are some monitoring data that suggest degradation to other chlorinated alkenes (HSDB, 1993).

H.1.17.4 Pharmacokinetics (Routes of Exposure, Distribution, Absorption, Transport, and Degradation)

Inhaled trichloroethene is rapidly and extensively absorbed from the respiratory tract of humans with a leveling off in the absorption rate occurring after about 8 hours of exposure (ATSDR, 1988). No studies are available on the absorption of TCE from the human gastrointestinal (GI) tract, but considering the high lipophilicity and numerous reported cases of poisonings, extensive GI absorption seems likely (ATSDR, 1988). Animal studies show that 90-100 percent of TCE is absorbed from the GI absorption with peak blood levels occurring within 3 hours (ATSDR, 1988). Distribution of TCE in humans is available only from pharmacokinetic models which generally predict the highest concentrations occurring in adipose tissue (ATSDR, 1988). This is supported by animal studies demonstrating high TCE levels in fat and blood with essentially no TCE detected in other tissues (ATSDR, 1988). Once absorbed, TCE is readily metabolized in the liver by the mixed function oxidase system to a reactive epoxide intermediate, which is subsequently reduced to excretion metabolites by the enzyme by epoxide hydrolase (Fawell and Hunt, 1988). In humans, elimination of TCE occurs predominantly in urine as metabolized TCE, while exhalation of unchanged and metabolized TCE and elimination in feces are other less important routes of elimination (ATSDR, 1988). Studies of exposed humans and animals show that approximately 90 percent of the urinary TCE metabolites detected consist of trichloroacetic acid, trichloroethanol, and conjugated trichloroethanol However, elimination of unchanged TCE in exhaled air appears to be the major route of elimination of TCE in experimental animals.

H.1.17.5 Acute Toxicity

The primary target organ of acute exposures to TCE in humans is the central nervous system (CNS) where it exerts a depressant effect (Fawell and Hunt, 1988). TCE in air at concentrations

ranging from 5,000 to 20,000 ppm have been used to produce a mild anesthesia in humans (Proctor et al., 1988). Volunteers exposed to 500 to 1000 ppm experienced CNS depression characterized by dizziness, lightheadedness, lethargy and impairment of visual-motor test (Proctor et al., 1988). No signs of toxicity or impaired performance have been observed at 300 ppm. The high lipid-solubility of TCE facilitates in entry into the CNS where it is thought to alter lipid composition of myelin, leading to nerve degeneration (Fawell and Hunt, 1988). The oral LD_{50} LD in rats has been reported at 4920 mg/kg (Torkelson and Rowe, 1982).

H.1.17.6 Chronic Toxicity

Excessive chronic occupational exposure to TCE is also predominantly associated with CNS disturbances such as headaches, dizziness and impaired touch and pain sensitivity (Fawell and Hunt, 1988). Also, in an old occupational study, altered heart muscle conduction was reported in dry-cleaning workers exposed to high levels of TCE (Vyskocil, 1953). Chronic dermal contact may cause chapping and erythema (reddish skin) due to skin defatting. In animal studies, hepatotoxic effects were noted (depressed liver glucose-6-phosphate activity) at doses of 800 mg/kg/day (Buben and O'Flaherty, 1985). Also, pathological changes were seen in the kidneys of mice and rats administered TCE orally at a dose of 1000 mg/kg 5 days/week for 103 weeks (NTP, 1983).

H.1.17.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity

TCE was found to increase DNA synthesis (both with and without metabolic activation) in human lymphocytes in vitro (Percocco and Prodi, 1981). Also, one study found an increase in hypoploid cells (deficient number of diploid chromosomes) in workers exposed to TCE at levels up to 75 ppm for 1 to 21 years (Konietzko et al., 1978), while Gu et al. (1981) reported increase in sister chromatid exchange in six workers exposed to unknown concentrations of TCE. Other in vitro assays using bacterial or animal cell lines have been negative without metabolic activation and positive following metabolic activation (ATSDR, 1988).

Carcinogenicity

At present, epidemiological studies on the carcinogenic potential of inhaled TCE have provided inadequate evidence due to low cohort sizes, concurrent exposures with other carcinogens and short follow-up periods (Fawell and Hunt, 1988). However, a controversial study found an association between TCE contaminated wells and increased incidence of childhood leukemias in Woburn, MA (Lagakos et al., 1986). This study was criticized for several methodological flaws. The National Cancer Institute administered TCE orally to mice at doses up to 2400 mg/kg for males and up to 1800 mg/kg for females 5 days/week for 78 weeks resulting in a significant increase in hepatocellular carcinomas and a slight increase in lung tumors in both sexes at high doses (NCI, 1976). No liver tumors were seen at doses of 500 mg/kg or 1000 mg/kg. In an inhalation study, a significant increase in the incidence of lung adenocarcinomas were observed in mice exposed to 150 ppm and 450 ppm TCE 7 hours/day, 5 days/week for 104 weeks (Fukuda et al., 1983). No tumors were observed in rats similarly exposed. The EPA has categorized trichloroethene as a probably human carcinogen (Group B_2) based on a weight-of-evidence scheme (EPA, 1989a).

Teratogenicity (and other reproductive effects)

No reports of reproductive or developmental effects of TCE in humans are available with the exception of the controversial study of Lagakos et al. (1986) mentioned in the carcinogenicity section. In this study, a statistical association was found between access to well water containing various hydrocarbons, including trichloroethene (267 ppb), and perinatal death and congenital malformations (ATSDR, 1988). However, numerous methodological criticisms have been published leaving an uncertain conclusion from the results of this study. Animal studies have produced mixed results. Decreased sperm motility (45 percent) in mice and impaired copulatory behavior in rats were observed after a 1 week exposure to 1000 mg/kg (Zinick et al., 1984). Animals studies on developmental effects are unremarkable. Fetotoxic (a reversible delayed development), but not teratogenic effects have been observed in mice, although there are inconsistencies in the low-observed effect level (ATSDR, 1988).

H.1.17.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

In EPA's issue papers from the Environmental Criteria and Assessment Office (ECAO), Superfund Health Risk Technical Support Center (USEPA, 1993b), trichloroethene is classified in the C-B2 continuum. The inhalation unit risk value is 1.7E-06 $(\mu g/m^3)^{-1}$.

EPA Dose-Response Parameters

The EPA has not promulgated any dose-response parameters for trichloroethene.

Trichloroethene has caused carcinogenic responses in rats exposed by gavage and in mice exposed by inhalation. Trichloroethene also acts as a central nervous system depressant following both acute and chronic exposure by both ingestion and inhalation pathways. Occupational exposure to concentrated trichloroethene vapors may result in dermatitis.

H.1.17.9 References

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H.1.18 Trichlorofluoromethane

H.1.18.1 Background

Trichlorofluoromethane (TCFM), also known as Freon-11, is one of the more toxic of the fluorocarbon compounds (Sax 1975). Its primary uses have been as an aerosol propellant, refrigerant and blowing agent for polymeric foams.

H.1.18.2 Pharmacokinetics

Both absorption and elimination of TCFM are relatively rapid in humans and experimental animals (NIOSH 1983). For example, dogs exposed to 10,000-30,000 ppm TCFM for four to five minutes exhaled the major portion within the first two minutes (Balke et al. 1974). In a study of dogs exposed to 1000 ppm TCFM, 77% of the inhaled dose was absorbed after an eight hour exposure (Adir et al. 1975).

The cardiovascular and bronchopulmonary actions of trichlorofluoromethane are its two most important toxicological features. These mechanisms are considered to be mediated in part by metabolic products that bind to lipid and protein cell constituents. These products in turn affect vital processes such as cellular oxidation (USEPA 1987).

H.1.18.3 Acute Toxicity

TCFM acts primarily like a weak narcotic (Sax 1975). The lowest reported LC50 in the available literature is 26,200 ppm, based on a study of rats exposed to TCFM for 4 hours (ACGIH 1980). During exposure, sublethal doses caused rapid respiration with some mild hyperactivity, while lethal doses caused hyperactivity, tremors, inactivity, irregular respiration and death within four hours.

Laboratory animals periodically exposed to high concentrations for several days may exhibit biochemical changes consistent with slowing of cellular oxidation. Furthermore, studies with experimental animals suggest that inhalation exposures to high concentrations of trichlorofluoromethane may produce various cardiovascular and circulatory abnormalities.

Mild central nervous system depression and irritation of the upper respiratory tract have been reported in humans exposed to very high concentrations of TCFM (Clayton and Clayton 1981-1982). Cases of severe intoxication, cardiac arrhythmia and death have been reported under such circumstances (Sax 1975). Early human experience indicated that exposure to high vapor concentrations of TCFM (e.g. 20%) may cause reversible effects such as confusion, pulmonary irritation, tremors and coma (Gosselin et al. 1984). TCFM inhalation studies in mice, guinea pigs, dogs, and monkeys have produced similar toxic effects (NRC 1977, Clayton and Clayton 1981-1982).

H.1.18.4 Chronic Toxicity

Rats and rabbits exposed to 50,000 ppm for one hour twice daily for 15 days showed increased blood glucose and lactic acid, decreased oxygen uptake and other biochemical changes consistent with slowing of cellular oxidation. Comparable exposure at 25,000 ppm did not induce these changes. Both a 4 week series of 3.5 hour exposures to 12,500 or 25,000 ppm and two 6-week studies with 6 hour exposures to 4000 ppm and 10,250 ppm showed no effects attributable to trichlorofluoromethane in various species of laboratory animals. Monkeys, dogs, rat and guinea pigs exposed continuously at 100 ppm for 90 days showed no specific abnormalities attributable to FC-11. A slight increase in urinary fluoride was seen in rats fed for 90 days at 450 mg/kg, but not at 200 mg/kg; dogs showed no effects when fed 170 mg/kg or 350 mg/kg.

Carcinogenicity

Based on limited available animal data, trichlorofluoromethane does not appear to have carcinogenic potential. Two year studies in rats and mice fed approximately 500 or 1000 mg/kg and 2,000 or 3900 mg/kg, respectively, yielded no significant increase in tumor incidence (NCI 1978). However, results obtained for the rats in this study can not be considered conclusive due to insufficient sample size and the early mortality of exposed animals.

Mutagenicity

Results of mutagenicity tests of TCFM has been negative in Salmonella typhimurium (Zeiger et al. 1987). Although genotoxicity data are scant, trichlorofluoromethane exhibits no mutagenic

activity in Salmonella tester strains (ICF 1985). An Ames bacterial mutagen test was also negative (TLV DOC).

Reproductive/Developmental Effects

Little data are available concerning the potential reproductive effects of TCFM exposure in humans or animals. The only available study involved rats and rabbits exposed to a 9:1 mixture of Freon-12 and TCFM (NCR 1977); no embryotoxic r teratogenic effects were observed in rats or rabbits exposed by inhalation to 20,000 ppm of . But what was the endpoint in this study not clear the extent tho which this endpoint was evaluated.

Sensitive Populations

No information was available to identify potentially sensitive human populations.

Chemical Interaction

No reports were located which would suggest that the toxic effects of trichlorofluoromethane are influenced by exposures to other chemicals.

Dose-Response Parameter Estimates

The dose-response parameter estimates for carcinogens and noncarcinogens are computed differently by the EPA; therefore these estimates are presented separately below.

Carcinogenic Effects:

There is no evidence available to suggest that trichlorofluoromethane is carcinogenic in either humans or laboratory animals. The EPA has consequently not derived an estimate of the dose-response relationship. Therefore, the carcinogenicity of trichlorofluoromethane was not quantitatively evaluated in this assessment.

Noncarcinogenic Effects:

The EPA has derived an oral reference dose (RfD) of 3×10^{-1} mg/kg/day for trichlorofluoromethane (USEPA, 1990a) based on the identification of a LOAEL

(lowest-observed-adverse-effect-level) of 349 mg/kg/day in a cancer bioassay in rats and mice (NCI, 1978). The critical effect observed at this dose was reduced survival and histopathological abnormalities. An uncertainty factor of 1000 was incorporated (10 to convert subchronic effects to its chronic equivalent), 10 to account for uncertainties in extrapolating animal data to humans, and 10 to account for sensitive human subgroups.

The Office of Health and Environmental Assessment has derived an inhalation RfD of 2×10^{-1} mg/kg/day (USEPA, 1990b) based on elevated BUN (blood urea nitrogen) and lung lesions in dogs continuously exposed to trichlorofluoromethane at 5600 mg/m^3 for 90 days (Jenkins et al. 1970). An uncertainty factor of 10,000 was incorporated into the development of the RfD as described above with an additional factor of 10 to convert subchronic effects to a chronic equivalent.

Oral RfD: 3×10^{-1} mg/kg/day (USEPA, 1990a).

Inhalation RfD: 2×10^{-1} mg/kg/day (USEPA, 1990b).

H.1.18.5 References

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H.1.19 1,1,2-Trichloro-1,2,2-Trifluoroethane

H.1.19.1 Health Effects

In acute toxicity studies, human subject experienced significant impairment of dexterity and vigilance after exposure to 4,500 ppm trichlorotriflouroethane (TCTFE) for 30 to 100 minutes (Stopps et al., 1967). In another acute study, human exposures of 6 hours daily, 5 days/week for 2 week at concentrations of approximately 500 and 1,000 ppm caused mild throat irritation (Imbus, 1972). The LC50 for 2-hour exposures of experimental animals ranged from 50,000 to 120,000 ppm (Aviado, 1975). Chronic exposure of rats and rabbits to 12,000 ppm for up to 2 years caused no adverse effects (Fawell and Hunt, 1988). A reported LD_{50} for TCTFE in rats was 43 gm/kg (RTECS, 1987). There is little information to indicate TCTFE exhibits mutagenic, carcinogenic or reproductive effects.

H.1.19.2 Dose-Response Parameter Estimates

The dose-response parameter estimates for carcinogens and noncarcinogens are computed differently by the EPA; therefore, these estimates are presented separately below.

Carcinogenic Effects:

There is no evidence available to suggest that trichlorotrifluoroethane is carcinogenic to either humans or laboratory animals. Therefore, the carcinogenic effects of trichlorotrifluoroethane were not quantitatively evaluated in this assessment.

Noncarcinogenic Effects:

The EPA has developed an oral reference dose (RfD) for trichlorotrifluoroethane of 30 mg/kg-day (EPA, 1990). This dose was based on an inhalation study in which occupational exposure of humans at concentrations of 5,338 mg/m^3 for 2.77 years experienced no apparent adverse effect (NOAEL) (EPA, 1990). An uncertainty factor of 10 accounts for the expected interhuman variability to the toxicity of this chemical in lieu of specific data (EPA, 1990). An inhalation RfD is not available.

Oral RfD: 30 mg/kg-day (EPA, 1990).

H.1.19.3 References

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H.1.20 2,4,6-Trinitrotoluene

H.1.20.1 Occurrence and Use

2,4,6-Trinitrotoluene (TNT) is used as an explosive.

H.1.20.2 Physical and Chemicals Properties of TNT

Molecular Weight	227
Water Solubility	Sparingly soluble

Source: The Merck Index, 1989

H.1.20.3 Absorption, Distribution, and Excretion

TNT was absorbed in rats, mice, rabbits, and dogs following oral, dermal, and intratracheal administration of a single dose (HSDB, 1994). The most extensive absorption occurred after intratracheal instillation. Excretion was primarily in urine and to a lesser extent in feces.

In workers at two explosives factories, TNT was shown to be absorbed rapidly during the exposure period. A wide variation in the rate of metabolite clearance was observed (HSDB, 1994).

H.1.20.4 Acute Toxicity

TNT may cause irritation of the eyes and skin among munitions workers exposed to its dust or vapor (HSDB, 1994). No additional information regarding specific acute toxicity tests relevant for human exposures was found.

H.1.20.5 Chronic Toxicity

Cataracts have been diagnosed in a considerable proportion of chronically exposed workers (HSDB, 1994). Severe hepatic disease caused by exposure to TNT was recorded among workers in munitions factories during the two World Wars. EPA has not developed a chronic oral or inhalation reference dose for TNT.

Dogs, mice, and rats were dosed daily in their diets with alpha-TNT for up to 13 weeks by capsule. Dogs were dosed at 0, 0.2, 2.0, or 20 mg/kg; rates received 0, 0.002, 0.01, 0.05, or 0.25%, and mice received 0, 0.001, 0.005, 0.025, or 0.125%. All species receiving the highest doses exhibited anemia, with reduced erythrocytes, hemoglobin, and hematocrit. Alterations in organ weight, including enlarged spleens and livers, and depressed body weight and/or body weight gain were observed. Reduced testes size was observed in rats. Also, anemia was present at intermediate dose levels.

H.1.20.6 Mutagenicity, Carcinogenicity, and Teratogenicity

2,4,6-TNT gave positive responses in the P388 mouse lymphoma gene mutation assay in the absence of auxillary metabolic activation. It gave negative results when an activation system was included. Thus, TNT is a potential rodent liver carcinogen. EPA has not developed an oral or inhalation cancer slope factor for TNT.

H.1.20.7 References

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H.1.21 Vanadium

H.1.21.1 Occurrence and Use

Vanadium is a naturally occurring element in the earth's crust. Typical levels in pristine soils range from 60 to 110 mg/kg (Kabata-Pendias and Pendias, 1987). Vanadium also occurs naturally in fuel oils and coal. In the environment it is usually combined with other elements such as oxygen, sodium, sulfur, or chloride. The forms of vanadium most likely to be found at hazardous waste sites are not well known. One man-made form, vanadium oxide is most often used by industry, mostly in making steel. Much small amounts are used in making rubber, plastics, ceramics, and certain other chemicals (ATSDR, 1991).

H.1.21.2 Physical and Chemical Properties of Vanadium

Molecular Weight	50.94
Water Solubility, mg/l	0.0E+00
Bioaccumulation Factor for Fish	1.0E+01
Bioaccumulation Factor for Shellfish	3.0E+03

Source: Multi-Media Exposure Assessment Manual, 1989

H.1.21.3 Environmental Fate and Transport

The global biogeochemical cycling of vanadium is characterized by releases to the atmosphere, water, and land by natural and anthropogenic sources, long-range transportation of particles in both air and water, wet and dry deposition, adsorption, and complexing. Vanadium generally enters the atmosphere as an aerosol. Anthropogenic releases of vanadium to the atmosphere are in the form of simple or complex vanadium oxides. Vanadium transported within the atmosphere is eventually transferred to soil and water on the earth's surface by wet and dry deposition and dissolution in sea water. Eventually, in the course of biogeochemical movement between soil and water, these particulates are adsorbed to hydroxides or associated with organic compounds and are deposited on the sea bed. The most likely way for vanadium to get into the environment is when fuel oil is burned. Anthropogenic releases of vanadium to the air account for approximately two-thirds of all vanadium emissions (ATSDR, 1991).

H.1.21.4 Routes of Exposure, Absorption, Distribution, Transport, and Degradation

The general population is exposed to background levels of vanadium primarily through ingestion of food. Workers in industries processing or using vanadium compounds are commonly exposed to higher than background levels via the inhalation pathway. Exposure through inhalation is also of importance in urban cities burning large amounts of residual fuel oil. Other populations possibly exposed to higher than background levels include those ingesting foodstuffs contaminated by vanadium-enriched soil, fertilizers, or sludge. Population in the vicinity of vanadium-containing hazardous waste sites may also be exposed to higher than background levels (ATSDR, 1991).

Absorption of vanadium compounds through the lungs is estimated to be about 25 percent for soluble compounds, while ingested vanadium is more poorly absorbed, on the order of 2-3 percent (ICRP, 1960). The largest storage compartment in the body is fat, followed by, and to a lesser extent, bone and teeth (Goyer, 1986). The principal tissues and organs to which vanadium and its compounds are distributed have been reported to include fat, bone, teeth and lungs. Most absorbed vanadium is excreted in the urine within one day following long-term moderate exposure to the dust (ATSDR, 1991).

H.1.21.5 Acute Toxicity

Acute exposure of human volunteers to 0.1 to 1 mg/m3 of vanadium pentoxide stimulates mucous secretions and coughing (Carson et al., 1986). Acute vanadium exposures in animals generally produce effects on the nervous system, hemorrhage, paralysis, and respiratory depression (Goyer, 1986).

H.1.21.6 Chronic Toxicity

A hypersensitivity reaction has been reported in individuals repeatedly exposed. Occupationally exposed individuals experienced respiratory tract irritation, dermal disorders, sneezing, sore throat, chest pain, and conjunctivitis (eye irritation) (Lagerkvist et al., 1986). Chronic exposure to high concentrations of airborne vanadium is believed to lead to chronic bronchitis, chronic rhinitis (nasal inflammation), and pharyngitis (inflammation of the pharynx) (Lagerkvist et al.,

1986). The formation of allergy-like eczematous skin is associated with chronic respiratory exposures in humans and animals (NAS, 1977). Kiviluoto (1980) investigated radiographs and pulmonary function test results of exposed and unexposed workers and found that there was no difference between unexposed workers and those with long-term occupational exposure to vanadium. However, they did note that exposed workers complained more frequently of wheezing. In animals, fatty changes and partial necrosis of the liver was observed following long-term inhalation exposure to van' ium pentoxide, trioxide and chloride (Lagerkvist et al., 1986). There is no evidence of chronic oral toxicity (NAS, 1977).

H.1.21.7 Mutagenicity, Carcinogenicity, and Teratogenicity

Mutagenicity and Carcinogenicity

There is no evidence that vanadium compounds are mutagenic, nor are they considered to be carcinogenic (Lagerkvist et al., 1986)

Teratogenicity

Very little data is available on the reproductive and developmental effects of vanadium compounds. However, two reports have reported skeletal abnormalities in offspring of hamsters and mice injected with vanadate during mid-gestation (Carlton et al., 1982, Wide, 1984).

H.1.21.8 EPA Carcinogenic Classification and EPA Dose-Response Parameters

EPA Carcinogenic Classification

The EPA has not classified Vanadium in terms of carcinogenicity.

EPA Dose-Response Parameters

There are no dose-response parameters for Vanadium reported in IRIS (1994). HEAST 1993 reports oral RfDs of 7.0E-03 mg/kg/day for vanadium, 9.0E-03 mg/kg/day for vanadium pentoxide, and 2.0E-02 mg/kg/day for vanadium sulfate.

H.1.21.9 References

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APPENDIX H2

Ecological Toxicological Profiles

LIST OF ACRONYMS AND ABBREVIATIONS

µg/day	Micrograms per day
µg/m^3	Micrograms per cubic meter
µg/ml	Micrograms per milliliter
µM	Micromole
Ag	Silver
As	Arsenic
Cd	Cadmium
COC	Contaminant of Concern
Cu	Copper
EC_{50}	Effects Concentration 50
EPA	U.S. Environmental Protection Agency
Hg	Mercury
IAA	Indoleacetic acid
LOAEL	Lowest observed adverse effects level
mg/kg	Milligrams per kilogram
mg/l	Milligrams per liter
NOAEL	No observed adverse effects level
NOEC	No observed effect concentration
Pb	Lead
ppb	Parts per billion
ppm	Parts per million
RNA	Ribonucleic acid
Zn	Zinc

This appendix presents profiles of the toxicity of arsenic, cadmium, copper, lead, mercury, silver, and zinc to plants and terrestrial vertebrate animals. These are the contaminants of concern (COCs) selected for biota from the chemicals that occur in the Group 2 SWMUs (3, 5, 8, 9, 30, and 31) at Tooele Army Depot-South. The profiles are adapted from DOE (1992) and EBASCO (1994).

1.0 ARSENIC

Arsenic is widely distributed in the environment in both trivalent and pentavalent forms, which differ in their fate, movement, and action. Human input of arsenic into the environment results from smelting, coal burning, and the use of arsenical pesticides (wood preservatives, leaf desiccants, herbicides, and insecticides).

Arsenic (As) occurs naturally in living organisms, but no confirmed physiological function has been attributed to this metal. Arsenic exhibits two inorganic forms with differing toxic properties. Arsenic III is known to bind to sulfhydryl groups on proteins, disrupting their function. The mechanism of arsenic V toxicity is less well known, but it does not bind to sulfhydryl groups. It does appear to selectively uncouple oxidative phosphorylation, poisoning aerobic adenosine tri-phosphate (ATP) generation. Under acidic conditions, arsenic III will slowly oxidize to arsenic V.

1.1 TERRESTRIAL VEGETATION

Arsenic occurs in virtually all soils and natural waters. Plants have therefore evolved in the presence of arsenic ions, and it is possible that arsenic is an essential element for plant growth. However, beneficial effects of arsenic on plants have not been documented. Arsenic is chemically similar to phosphorus, which is an essential plant nutrient.

Arsenic accumulation in plants is variable, depending on solubility of the arsenicals and soil properties. If sufficient arsenic is absorbed, plants may be killed. Alternatively, arsenic may accumulate in plant biomass and enter the food chain (Treshow 1978).

The uptake mechanism of arsenic to plants has been reported (NAS 1977). When arsenic in solution penetrates the cuticle of the root and enters the apoplast system, it bathes the external surface of plasmalemma of the symplast. This is the location of at least some of the enzymes of the living plant. One of the first symptoms of injury by sodium arsenite is wilting (loss of

turgor), which suggests an alteration in membrane integrity or permeability. Arsenites are more toxic than arsenates. The arsenate symptoms include yellowing (chlorosis), but not rapid loss of turgor. Arsenate is known to uncouple phosphorylation, thus impeding the availability of ATP to the plant. Arsenic and its derivatives are most commonly used in plant herbicides because of these pathway effects.

Callahan and Shepard (1991) studied the toxic effects of arsenic on large crabgrass (*Digitaria sanguinalis*), annual bluegrass (*Poa annua*), and creeping bentgrass (*Agrostis palustris*) via the soil. Poor germination of seeds and poor regrowth of adult plants was observed for annual bluegrass and large crabgrass when concentrations of arsenic totaled more than 136 kilograms per hectare (kg/ha) (based on soil residue build-up). The same effects were observed for creeping bentgrass when concentrations in the soil were greater than 272 kg/ha.

Field data on the effects of arsenic on grasses indicate toxic effects on plants at a concentration of 19 μg/g. These toxic effects were expressed as expressed as growth reduction.

Generally, nonnatural arsenic is introduced into the environment and growth media as an organic arsenical (i.e., herbicide). The NAS (1977) found that arsenic at soil concentrations of 1-4 parts per million (ppm) caused shotholing and defoliation of leaves in peach trees. Woolson (1973) studied uptake and phytotoxicity in green beans, lima beans, spinach, cabbage, tomatoes, and radishes. These vegetables had no growth in soil with arsenic concentrations of 500 ppm, where arsenic was applied via spray solutions to the plants and the soil.

Most studies have focused on the relationship between arsenic and phosphorus. Everett (1962) indicated that phosphorus increased the arsenic content of bluegrass and crabgrass in a turf treated with tricalcium arsenate. However, he found that phosphorus reduced absorption of tricalcium arsenate (measured as arsenic) from nutrient solutions from 246 to 29 ppm. He found

a potential species difference from the results of his study. Sckerl (1968) found that phosphorus reduced arsenic toxicity.

Arsenic also seems to have an interactive relationship with zinc. Batjer and Benson (1958) showed that toxicity in peaches grown in arsenic-contaminated soils could be reduced by foliar applications of zinc or iron chelates or soil applications of zinc or iron sulfates. The relationship is not completely clear, but Burleson and Page (1967) suggested that, with absorption of more than optimal phosphorus, phosphorus, and zinc reacted together in a manner that reduced either their mobility or their solubility. There may be an interactive relationship between arsenic, phosphorus, and zinc that enhances or minimizes toxicity of arsenic in soil to plants.

Very little food web modeling has been performed with arsenic as a primary analyte. Arsenic seems to be of more interest for its interactive properties with other plant nutrients. The distribution of arsenic through the food chain is greatly limited by its phytotoxic effects. That is, plant injury would generally occur if concentrations toxic to wildlife could be reached.

1.2 TERRESTRIAL VERTEBRATES

Little information is available on the effects, toxicity, and potential for accumulation as in terrestrial vertebrates. Absorption from the gastrointestinal tract is almost complete, as only 6 to 9 percent of orally administered arsenic-labeled trivalent or pentavalent arsenic is eliminated in feces in mice (Vahter and Norin 1980). Normal values for arsenic in whole blood and urine in humans are less than 10 µg/l and 50 µg/l, respectively. Excessive exposure is 50 µg/l in whole blood and greater than 100 µg/l in urine (Goyer 1986).

A modest accumulation of arsenic is seen in small mammals from orchards where lead arsenic was used as a fungicide. White et al. (1977) reported concentrations in European starling (*Sturnus vulgaris*) whole bodies (less skin, wings, and bill) of 0.019, 0.156, 0.171, and 0.139 µg/g. Details of experimental design were not provided with these data. Van Vleet (1982), in

a study of selenium-vitamin E deficiency in ducklings, identified a lowest observable adverse effects dose concentration of 18.9 µg/g. Byron et al. (1967) dosed rats and dogs for two years with sodium arsenite or arsenate. They observed pathologic changes in rats at 31 ppm in diet, or a dose of 1.5 µg/g-bw/day.

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2.0 CADMIUM

Cadmium (Cd) has been known as an element since 1817 and used extensively in industry since the 1930s. It is primary used for electroplating or galvanizing, as a color pigment for paints and plastics, and as a cathode material. It is also a byproduct of zinc and lead mining and manufacturing.

The significance of acclimatization to ambient metal concentrations is well illustrated by Cd. While many species may occur in areas where naturally occurring Cd concentrations fall within the range of acute toxicity values derived from laboratory toxicity testing (Eisler 1985), sublethal effects of Cd on individual organisms, populations, and communities are also documented.

Heavy metal ratios in native fauna are inconsistent with those of indigenous soil and vegetation, reflecting differences in relative mobilities. For both carnivores and herbivores, Cd is accumulated at rates greater than lead and zinc (Roberts and Johnson 1978) and therefore appears to bioconcentrate.

2.1 TERRESTRIAL VEGETATION

Cd is thought to be one of the most toxic elements for plants. Taylor et al. (1991) introduced wheat to various levels of Cd in soil media and determined the threshold to be 0.02 micromole (μM), which translates to a 152 percent growth reduction per μM. Cd was found to be more toxic to wheat than aluminum, copper, manganese, nickel, and zinc.

Adema and Henzen (1989) determined EC_{50} values (the concentration at which the weight of the plants is half that of the control plants) and no observed effect concentration (NOEC) values of Cd for growth of lettuce, oats, and tomatoes in loamy soil. EC_{50} values for lettuce, oats, and tomatoes were 33, 159, and 171 milligrams per kilogram (mg/kg), respectively. NOEC values for these plants were 3.2, 10, and 32 mg/kg, respectively; the mean of these NOEC values is 15.1 mg/kg.

The effect and accumulation of Cd in lettuce (*Lactuca sativa*) grown in hydroponic solution was found to be affected by the concentration of other trace elements. Consequently, no absolute toxicity limits for Cd can be drawn without considering other trace elements (Thys et al. 1991). Calcium, phosphorus, zinc, copper, and manganese reportedly impede Cd uptake. However, the results were not conclusive and seemed to depend on several other factors such as plant species and varieties.

OECD (1979) found that Cd caused reductions in yield in eight agronomic plants grown hydroponically. Three-week old plants showed 50 percent growth reduction over a subsequent 19-day period of treatment with Cd ions, as follows: beans, beets, turnips—0.2 milligrams per liter (mg/l); corn and lettuce—1.0 mg/l; tomatoes and barley—5.0 mg/l; and cabbage—9.0 mg/l.

The Cd content in surface agricultural soils has been found to range from traces to 4.67 mg/kg, with an average of 0.88 $\pm$ 0.79 mg/kg in 33 soils. The common natural level for Cd in soils is probably 1 mg/kg (OECD 1979). Cd concentrations in soil above 250 mg/kg (dry weight) may cause partial elimination of soil microflora (OECD 1979). Few studies of bioaccumulation and food web dispersal have been conducted involving plants and Cd. Because toxic Cd levels are known for soil microflora, it is possible that plants are affected by poor soil conditions long before Cd levels within the plant can reach toxic concentrations.

2.2 TERRESTRIAL VERTEBRATES

Wildlife are exposed to Cd primarily via ingestion of contaminated food and drinking water. In some situations, Cd contamination can occur mainly from aerial deposition (Beyer et al. 1985). Contamination is most severe near smelters and urban industrialized areas. Birds and mammals appear to be less sensitive to Cd than aquatic organisms. In kidney and liver tissues contamination may be aggravated by a protein (as metallothionein) and rendered less toxic (Klassen et al. 1986). Cd accumulates with age (Hunter et al. 1981) and is seen at higher

concentrations in insectivores such as common shrews (*Sorex araneus*) than in herbivores such as field voles (*Microtus agrestis*) (Roberts and Johnson 1978; Scanlon 1979).

Sublethal effects of Cd on birds and mammals include reduced growth rate, anemia, hypoplasia in bone marrow and gonads, enlarged heart, and behavioral impacts to adults and progeny. Lowest concentrations of Cd producing significant effects include cardiovascular disease in domestic pigeons (*Columba livia*) exposed to 600 parts per billion (ppb) Cd in drinking water and behavioral alterations of progeny after female black ducks (*Anas rubripes*) were fed 4 parts per million (ppm) Cd in their diets (Eisler 1985). Threshold concentrations of dietary Cd having significant physiological effects appear to be around 20 ppm for mallard (*Anas platyrhynchos*) ducklings, with exposures of adult birds ranging up to 75 ppm. Male and female mallards fed 200 ppm dietary Cd survived with no weight loss, but egg production was decreased in females (White and Finley 1978, cited in Eisler 1985).

Bone marrow and hematopoietic effects on rodents are known from dietary exposures of less than 2 ppm (Siewicki et al. 1983). The lowest oral dose causing mortality in laboratory rats and guinea pigs was 250 and 150 mg Cd per kg body weight, respectively. A maximum dietary Cd content of 100 microgram per kilogram (µg/kg) is recommended to avoid acute toxicity and effects of accumulation of Cd in tissues (EPA 1980, cited in Eisler 1985).

Eisler (1985) points out that U.S. Environmental Protection Agency (EPA) criteria for Cd in food for humans (75 micrograms per day [µg/day]) is probably not protective of wildlife, because birds and wild mammals consume 6 to 7 percent of their body weight per day and thus get a much higher dose than humans, who consume about 1 to 2 percent of their body weight each day.

Cd accumulates in liver and kidneys of vertebrates (Anderson and Van Hook 1973; Johnson et al. 1978). In humans, a Cd concentration of 200 ppm (fresh weight) in renal cortex tissue is the highest level at which no adverse effects are observed. Cd associated with the liver and kidney

of the chipping sparrow (*Spizella passerina*) was eliminated with a half-life of about 100 days. Mallard ducklings fed 20 ppm dietary Cd had accumulated 42 ppm Cd in liver tissue after 12 weeks. Mallards and chickens tolerated 200 ppm Cd in the diet for long periods, producing kidney concentrations of 130 ppm fresh weight.

Gray squirrels (*Sciurus carolinensis*) had higher Cd concentrations in their livers in urban areas (5.96 to 9.11 µg/g) than in rural areas (2.04 to 4.63 µg/g) (McKinnon et al. 1976). High concentrations were seen in kidney and liver tissues of rabbits by a smelting plant, 61 and 5.8 µg/g fresh weight, respectively (Gordon 1972). Meadow voles (*Microtus pennsylvanicus*) exposed to sewage sludge containing Cd for 4 years had fresh weight concentrations of 0.8 to 3.1 mg/kg in their livers and 3.5 to 19.1 mg/kg in their kidneys; in contrast, animals from control fields had 0.1 to 0.7 mg/kg in their livers and 0.3 to 1.1 mg/kg in their kidneys (Maly and Barrett 1984). Cd concentrations in the liver and kidney of common shrews, field voles, and wood mice were low (13.6, 20.5; 0.7, 1.7; and 0.4, 2.0 µg/g dry weight, respectively) at control sites, and significantly higher at a copper/Cd refinery (578, 253; 22.7, 88.5; and 18.2, 41.7 µg/g, respectively) (Hunter et al. 1981).

Whole body concentrations in the vicinity of zinc smelters, in dry weight for carcasses of 10 species of birds, was 2.5 mg/kg downwind and 1.2 mg/kg upwind (Beyer et al. 1985). For mice (*Peromyscus* sp.), values were 2.6 mg/kg downwind and 1.2 mg/kg upwind. For short-tailed shrews (*Blarina* sp.) values were 7.3 mg/kg downwind and 4.8 mg/kg upwind (Beyer et al. 1985). From uncontaminated sites, European starlings had whole body concentrations of 0.05 to 0.24 mg/kg fresh weight.

Cd residues in vertebrate kidneys or livers that exceed 10 mg/kg fresh weight or 2 mg/kg in whole body fresh weight should be considered probable Cd contamination. Levels of 13 and 15 ppm Cd tissue fresh weight probably represent a significant hazard to animals at higher trophic

levels. Residues of 200 ppm fresh weight kidney or more than 5 ppm whole animal fresh weight should be considered life-threatening (Eisler 1985).

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3.0 COPPER

Copper (Cu) is widely distributed in nature and is an essential element for both plants and animals. It has been used as a fungicide, has some human medicinal uses, and is used as a metal for such items as wire and cookware (because of its conductivity) and for water pipes. Copper contamination may enter soils and sediments as a result of smelting, mining, industrial activities, domestic waste emission, and the application of fertilizers, sewage sludge, algicides, fungicides, and molluscicides.

Copper (Cu) is a common trace element and an essential micronutrient necessary for a wide range of metabolic processes (Flemming and Trevors 1989). Copper is moderately soluble. Its bioavailability depends on a number of factors, such as pH, redox potential, soil and sediment type, water hardness, and organic content.

3.1 TERRESTRIAL VEGETATION

All higher plants require copper for the metabolism of nutrients (Berry 1975). Copper is highly interactive with other elements in soil. In acidic soils, copper is often out-competed by Al, causing low copper uptake in plants. The copper-iron balance seems to be important in

preventing copper deficiency in plants. A relationship has been found between copper, iron, and molybdenum which suggests that the balance of these ions may be more critical than the absolute amounts taken up by the plants themselves (Donahue et al. 1983).

Taylor et al. (1991) treated wheat with different concentrations of micronutrients in soil media. Growth reduction occurred at the threshold of 3.4 µM for copper. Copper caused a 19 percent growth reduction per µM at this threshold.

Rhoads et al. (1989) determined that copper concentrations of 150 mg/kg at soil pH less than 6.5 and 330 mg/kg at soil pH greater than 6.5 reduced growth of tomatoes (*Lycopersicon esculentum*). The study confirmed that copper is more available to plants in acidic soils if there is not an excess of Al present and, therefore, that the threshold for plants in toxic soils is lower.

Copper has low soil mobility, and the potential for copper accumulation is substantial over a period of time (Rhoads et al. 1989). Copper is strongly adsorbed to cation exchange sites, especially those on humus particles. Several plants, such as ***Viscaria alpina***, are copper tolerant and are able to grow on soils naturally rich in copper. Apices of the small lateral roots were either dead or abnormal with irregular branching of the roots at extremely high copper concentrations in the soil of 3,000 µg/g. Most of the copper in the plant was stored in the flower (Hansen and Gullvag 1984). It is not clear whether copper bioaccumulates in plants due to it's being bound in the soil, and what its inter-relationships with other ions in the soil are.

3.2 TERRESTRIAL VERTEBRATES

Copper is relatively nontoxic to mammals, and tolerance limits are generally 10- to 100-fold higher than for aquatic fauna. Rabbits, ponies, and pigs can tolerate high levels, 300 to 800 µg/g dry weight feed in their diets, with no toxicosis (Flemming and Trevors 1989). EPA levels acceptable in drinking water are 1.0 mg/l. Leach et al. (1990) studied broiler chicks fed diets

low in calcium and found an increased sensitivity to copper toxicity. Growth in these chicks was limited at a dose of 48 µg/g-bw/day.

At a zinc smelter, high concentrations of copper were found in short-tailed shrews (*Blarina*) and mice (*Peromyscus*). At this site, very little of the metal measured in the soil was incorporated in the plant foliage; most contamination in biota came from aerial deposition (Beyer et al. 1985).

Background dry weight concentrations of copper in whole body, liver, and kidney were 7.4, 14.6, and 19.7 µg/g in the field vole and 12.1, 23.7, and 30.7 µg/g in the common shrew, respectively. The granivorous wood mouse (*Apodemus sylvaticus*) had liver and kidney concentrations of 15.8 and 22.3 µg/g. At a copper refinery, concentrations in liver and kidney were 26.7 and 35.8 µg/g for the common shrew, 14.4 and 18.5 µg/g for the field vole, and 14.6 and 15.2 µg/g for the wood mouse, respectively (Hunter et al. 1989). Thus, the granivorous wood mouse and the herbivorous field vole showed no increase in copper content with the increased environmental copper levels. The predatory common shrew did experience significant copper accumulation, suggesting a potential for bioconcentration.

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4.0 LEAD

Historically, 98 percent of the lead (Pb) in the biosphere has come from automobile emissions, specifically the combustion of Pb alkyl additives in gasoline (Smith 1980). Introduced as a fine aerosol, Pb eventually falls out either in precipitation or in dust onto vegetation and soil. The prevalence of leaded gasoline until recent years has resulted in high accumulations of Pb along roadsides.

4.1 TERRESTRIAL VEGETATION

Elemental Pb is not taken up through plant roots (Treshow 1978), but in methylated form is bioavailable and more toxic (Klein and Scheunert 1978). Pb inhibits plant growth, reduces photosynthesis, and reduces mitosis and water absorption (Demayo et al. 1982).

For two species of roadside weeds (*Cassia* sp.), pollen germination was reduced by 90 percent and seed germination by 87 percent at Pb levels of about 500 mg/kg dry weight in soil and about 300 mg/kg dry weight in foliage (Krishnayya and Bedin 1986). Stournaras et al. (1984) had similar findings with a study of soybean (*Glycine max*) cells exposed to Pb. When the cells were exposed to Pb at concentrations of 207 µg/l, growth was inhibited before cells died.

Anderson (1977) concluded that several metals, including Pb, were generally unavailable for plant uptake. Eisler (1988) confirmed that uptake of Pb by terrestrial plants is limited by the low bioavailability of Pb from soils; adverse effects seem to occur only at total concentrations of

several hundred milligrams Pb per kilogram soil. EPA (1980) concluded that there is no evidence for biomagnification of Pb in the food chain that includes vegetation, cattle, dung, and dung beetles (Robel et al. 1981), nor is there convincing evidence that terrestrial vegetation is important in food chain biomagnification of Pb.

Although foliar uptake and translocation of lead nitrate has been demonstrated (Hemphill and Rule 1975), foliar uptake of particulate heavy metals is reportedly of minor importance in contributing to the metal concentrations in annual rings (Arvik and Zimdahl 1974). Little (1973) found that more than 90 percent of the heavy metal burden measured for the leaves of deciduous trees was in the form of surficial deposition that could be removed by washing the leaves in detergent or mild acid solutions.

4.2 TERRESTRIAL VERTEBRATES

The toxicity of Pb to mammalian systems is widely recognized. Much of the toxicity to vertebrates probably stems from its tendency to demyelinate axons. Pb also interferes with the activity of the adenosine tri-phosphate enzyme, ATP-ase, and thus is potentially toxic to all organisms (Jernelov et al. 1978). Toxic concentrations of Pb in vertebrates are mostly due to the ingestion of lead shot. More than one million ducks and geese die annually as a result of such ingestion (Clemens et al. 1975, cited in Eisler 1988). As with other biota, bioaccumulation is also the result of exposures to combustion of leaded gasoline in vehicles. Raptors, in turn, ingest Pb from dead or crippled game, from Pb-poisoned waterfowl that had ingested lead shot, or from roadside mammals and invertebrates that had high exposures. High Pb doses induce abortion, reduce or terminate pregnancy, result in stillbirths, or increase skeletal malformations. Pb toxicosis has been studied mostly in livestock and laboratory animals. Survival was reduced under the following regimens: acute oral doses of 5 mg/kg body weight in rats, chronic oral doses of 0.3 mg/kg body weight in dogs, and dietary levels of 1.7 mg/kg body weight in horses (Eisler 1988). The lowest dose of 0.3 mg/kg bw/day is approximately equal to a dietary concentration of 12 mg/kg.

Although ingestion of food containing biologically incorporated Pb is unlikely in itself to cause Pb poisoning (Stendell 1980; Custer 1984; Pattee 1984; all cited in Eisler 1988), the effects of lower exposure levels are not well known (Nriagu 1978). While the use of lead arsenate as an insecticide in orchards has decreased, residues remain in upper soil surfaces and will be bioavailable almost indefinitely (Gilmartin et al. 1985, cited in Eisler 1988). Sublethal effects such as a delayed impairment of learning and abnormal social behavior were seen in monkeys administered 0.1 milligrams Pb/kg body weight daily or fed diets containing 0.5 mg Pb/kg.

Differences in response to Pb contamination has been documented to differ based on species, age, season, geographic location, habitat, and the form in which the metal was ingested (Finley and Dieter 1978; Mudge 1983; Srebocan and Rattner 1988; all cited in Eisler 1988). Comparisons at different traffic densities found concentrations of Pb to be lowest in granivores, intermediate in herbivores, and highest in insectivores (Williamson and Evans 1972). Organic Pb has much greater impact than inorganic Pb compounds.

Concentrations of Pb in tissues in pigeons were highest in urban areas (Tansy and Roth 1970; Hutton and Goodman 1980) and close to highways (Getz et al. 1979). Starlings had whole body (less skin, bill, and wings) concentrations of 1.088 µg/g in urban areas and 0.681 µg/g in rural areas. Four bird species had higher Pb concentrations near a steel factory (27 µg/g) than farther from the factory (2.5 µg/g) (Dmowski and Karolewski 1979). Songbirds near zinc smelters had 56 ppm dry weight of Pb, and shrews had even higher concentrations. Two cuckoos from the same contaminated area had liver concentrations of 18 and 25 ppm, respectively, and appeared healthy (Beyer et al. 1985). In contrast, death resulted from Pb poisoning at liver concentrations of 23 to 38 mg/kg fresh weight in raptors (Pattee et al. 1981, cited in Eisler 1988).

The highest concentrations of Pb in kidney and liver tissues of mice near smelting plants was 110 and 23 µg/g, respectively (Gordon 1972). Shrews had even higher concentrations (110 ppm dry weight) than mice (17 ppm) near a zinc smelter. Kidney concentrations of Pb for the shrews

were 280 ppm wet weight, which was considered to be toxic (Beyer et al. 1985). Livers of horses whose death was a result of Pb contamination contained 5.7 and 4.4 μg/g, and kidneys had 6.5 and 4.8 μg/g. In humans, Pb levels of 20 ppm are considered high.

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5.0 MERCURY

Mercury (Hg) compounds have no known role in normal physiology, and their presence in the cells of living organisms apparently represents contamination from natural and anthropogenic sources. Researchers have had difficulty specifying threshold levels or toxic effects on the basis of present knowledge (NAS 1978).

5.1 TERRESTRIAL VEGETATION

All plants appear to accumulate traces of mercury, but the amount depends on the plant species, locality, and chemical form of mercury available. Rooted plants absorb elemental mercury and alkylmercurials much more readily than ionic inorganic mercury (Dolar et al. 1971). Siegel et al. (1971) reported root growth inhibition in cucumber seedlings grown in 1 ppm $HgCl_2$ solution. The bioaccumulation factor reported by Shariatpanahi and Anderson (1986) was 0.45 for vegetables and herbs. This would make a safe soil concentration (i.e., protective of plants) of 2 ppm and below. From this initial point of entry, terrestrial plants, mercury is substantively concentrated in the terrestrial food web. Bioaccumulation factors in birds range as high as 14 in the mallard (Heinz 1980) and as high as 22.5 in the mink (Wren et al. 1987).

5.2 TERRESTRIAL VERTEBRATES

The long-term use and subsequent ban in 1966 of alkyl mercury seed dressings in Sweden has provided some valuable comparisons of mercury concentrations. Concentrations in liver, muscle, and kidney of goshawks (*Accipiter gentilis*) in 1966 were 2.27, 0.99, and 3.06 µg/g, respectively. These same measurements, taken 8 years after the ban in 1974, were 0.5, 0.2, and 0.57 µg/g (Henrikson and Karppanen 1975). In starlings, mercury concentrations in whole bodies (less bill, skin, and wings) were 0.063 µg/g at the initiation of a ban on mercurial fungicides. Two years later, values had dropped to 0.02 µg/g (White et al. 1977). Concentrations of mercury in rodent livers were 1.248 µg/g in fields treated with mercury seed dressings and 0.18 µg/g in untreated areas (Fimreite et al. 1970).

Mammalian toxicity studies of mercury have reported reproductive effects and nonlethal effects after doses of organic mercury were administered. Cats dosed orally with 0.250 mg organic Hg/kg body weight/day for 48 days exhibited increased incidence of anomalous fetuses (Khera 1979, in Eisler 1987). Rats were also orally dosed with 0.50 mg organic Hg/kg body weight/day, and exhibited reduced fertility (Khera 1979, in Eisler 1987). Mink showed signs of poisoning after ingesting 1.100 mg organic Hg/kg in the diet (Kucera 1983, in Eisler 1987).

Avian mercury toxicity has also been studied. The effects level was reported for Japanese quail after the birds were fed 32.0 mg inorganic Hg/kg diet or 4.0 mg organic Hg/kg diet in a study that was conducted for 9 weeks from the time of hatching (Hill 1981, in Eisler 1987). Red-tailed hawks are about twice as sensitive to Hg toxicity as kestrels, magpies, and pheasants (Solonen and Lodenius 1984, in Eisler 1987). Adverse effects on mallard reproduction were observed from a diet of 0.5 mg/kg (Heinz 1979).

Chronic exposure of laboratory rats to inorganic mercury has resulted in decreased body weight and increased kidney weight. The central nervous system is a major target for organic mercury compounds. Adverse effects in humans to subchronic and chronic oral exposures include brain lesions, brain cell destruction, hearing and visual impairment, and loss of sensation to extremities.

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6.0 SILVER

Silver (Ag) is very toxic even in minute amounts to living organisms. Ag is a white, ductile metal occurring naturally in the pure form and in ores. Bowen (1979) suggested that Ag shows a close relationship between parent material and soil concentrations, which may have some relationship to bioaccumulation over time. Reported concentrations of Ag in parent materials are on the order of 0.05 μg/g, slightly lower than the average crustal abundance. Near smelters, power plants, and in sewage sludges, values of 0.3 μg/g can be expected. There appear to be no relevant data concerning the chemistry or mobility of Ag in soils (Coughtrey and Thorne 1983).

6.1 TERRESTRIAL VEGETATION

The Ag ion Ag^{+1} is an effective inhibitor of ethylene action in plants (Beyer 1976). Among the ethylene effects found by Beyer to be nullified or inhibited by the Ag ion were the etiolation of pea seedlings; promotion of abscission of leaves, flowers, and fruits of cotton; and induction of senescence in orchid flowers. Silver thiosulfate has proven to be even more effective in delaying senescence of cut flowers than silver nitrate (Halevy and Mayak 1981).

Hunter (1953) studied seasonal changes in the concentrations of many elements, including Ag, in fronds and rhizomes of the fern *Pteridium aquilinum*. He noted that concentrations of Ag increased gradually and were highest when the fronds were old, presumably because of exposure time. Bioaccumulation of Ag in plants apparently does occur. However, little work has been done on its movement through the food chain.

6.2 TERRESTRIAL VERTEBRATES

Ag does not occur regularly in animal tissues. The major effect of excessive absorption of Ag is local or generalized impregnation of the tissues, where it remains as silver sulfide. This forms an insoluble complex in elastic fibers, resulting in argyria (Goyer 1986). Although the data for the systemic distribution of stable Ag are variable, they do not suggest that any organ or tissue, except perhaps the spleen, concentrates the element to any great extent (Coughtrey and Thorne 1983). In a 12-week study, Walker (1971) reported a no observed adverse effects level (NOAEL) of 65 mg/kg/day for rats exposed to Ag in the diet. Venugopal and Lucky (1978) reported an LD_{50} for Ag metal colloid in mice at 100 mg/kg body weight, an LD_{50} for silver oxide in rats at 2820 mg/kg body weight, and an LD_{50} for silver fluoride in guinea pigs at 300 mg/kg body weight.

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7.0 ZINC

Zinc (Zn) is an essential metal, acting as a cofactor in many enzymes. Thus, it is not surprising that many organisms have systems to accumulate and store Zn. However, at concentrations above the micronutrient level required, Zn exerts toxic effects. Zn may enter a food chain through aerial deposition on foliage or through uptake by plant roots. Although Zn is extremely soluble, uptake by roots is limited.

7.1 TERRESTRIAL VEGETATION

Zn is an important micronutrient for plants. It is essential to the synthesis of the important plant hormone indole acetic acid (IAA) and may be involved in protein synthesis (Barbour et al. 1987).

Fungal hyphae of mycorrhizae growing from the plant roots into additional soil areas help to absorb many nutrients, particularly the less mobile nutrients such as Zn (Donahue et al. 1983). Excess soil phosphorus can cause Zn deficiency. In susceptible plants such as corn, beans, and flax, excess soluble phosphate precipitates Zn into insoluble zinc phosphates, both inside the plant and in the soil (Donahue et al. 1983). As with most metals, Zn is interactive with other elements in the soil. Micronutrient cations such as Zn are relatively insoluble in nutrient solutions when provided as common inorganic salts, and they are nearly insoluble in most soil solutions (Salisbury et al. 1985). This insolubility is especially marked if the pH is above 5 (Clark 1982).

Taylor et al. (1991) subjected wheat to various Zn concentrations in soil media. The wheat plants showed signs of growth reduction at a threshold of 37 µM. Using the Weibull frequency distribution, Zn caused 0.5 percent growth reduction/µM. Growth reduction occurred even at nearly neutral pH conditions (6.5) in the soil.

Surface application of Zn on rangelands having claypan soils could increase herbage production, but the Zn concentration could become toxic to the crown and roots of the grasses. White (1991) found that herbage decreased and chlorosis occurred in blue grama (*Bouteloua gracilis*) plants

when application rates exceeded 0.40 grams Zn per kilogram soil. At 2.0 grams Zn per kilogram soil applied as zinc chloride, one-half of the plants died (White 1991).

7.2 TERRESTRIAL VERTEBRATES

Beyer et al. (1985) found that very little of the Zn in soil was incorporated in flora and fauna; contamination came predominantly from aerial deposition. They also found higher concentrations of Zn in shrews and lower concentrations in mice, i n contrast to Roberts and Johnson (1978), who found similar values between these herbivores and insectivores. Kidney concentrations in gray squirrels were higher in urban areas (25.5 to 31.9 µg/g) than in rural areas (14.3 to 18.6 µg/g) (McKinnon et al. 1976).

Zn absorption is affected by numerous dietary factors. These interactions and the uptake mechanisms are generally not well understood. In a laboratory study, Zn was administered in drinking water (200 mg/l) by itself and in combination with other metals (Cooke et al. 1990). Resultant Zn concentrations in the kidneys were higher than liver and femur concentrations. However, this was also the case when the combinations Zn/Cd and iron/Pb/Zn/Cd were administered. In fact, the highest kidney concentrations occurred in the high Cd-only treatments. This may reflect the induction of metalliothioneins, which can bind Zn and Cd, and subsequent redistribution and accumulation in the kidney (Cooke et al. 1990).

Most animals have a high tolerance for Zn. Ruminants are more susceptible to Zn intoxication than monozootic animals. Beef cattle and lambs tolerate 500 mg of Zn/gm feed (Ott et al. 1966). Pigs and rats tolerate up to 0.10 percent Zn in diet, but when fed 0.5 percent Zn in diet, rats become anemic , grow poorly and have high mortality (Sutton and Nelson 1937, Lewis et al. 1957). Venogopal and Luckey (1978) reported LD_{50} values for oral exposure to Zn salts:

350 mg/kg body weight (zinc chloride—mice)
350 mg/kg body weight (zinc chloride—rat)

250 mg/kg body weight (zinc chloride—guinea pig)

45.7 mg/kg body weight (zinc phosphate—rat)

Drinker et al. (1927), Dughay et al. (1977) reported NOAEL 98.3 mg/kg body weight for Zn in rats and a LOAEL 38 mg/kg body weight/day for Zn in mice.

Zn seems to have a very low level of transfer potential through terrestrial food chains, which may be associated with its essential role in biological systems (Roberts and Johnson 1978).

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