Toxicity Profiles

Introduction

The toxicity profiles in this database were developed using information taken from the United States Environmental Protection Agency's Integrated Risk Information System (IRIS) and Health Effects Assessment Summary Tables (HEAST) and other regulatory sources. The profiles and their references are provided to eliminate the effort needed to produce the toxicity profiles presented in the toxicity assessment chapter of a risk assessment and to supplement the human health risk-based preliminary remediation goals presented elsewhere in the RAIS.

In this database, the toxicity profiles are presented in three formats: formal, condensed, and RAGS Part A.

> Toxicity profiles in the formal format are several pages long and are similar to the profiles found in IRIS.
>
> Toxicity profiles in the condensed format are generally less than a page in length and largely consist of the executive summary from the formal version.
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> Toxicity profiles in the RAGS Part A format, are maintained with current toxicity information and are designed for inclusion in the main body of a risk assessment. According to RAGS Part A, "A short description of the toxic effects of each chemical carried through the assessment in non-technical language should be prepared for inclusion in the main body of the risk assessment. Included in this description should be information on the effects associated with exposure to the chemical and the concentrations at which the adverse effects are expected to occur in humans. Toxicity values should be accompanied by a brief description of the overall data base and the particular study from which the value was derived. In addition, a notation should be made of the critical effect and any uncertainty factors used in the calculation. For any RfD value obtained from IRIS, a notation of the degree of confidence associated with the determination should also be included. To aid in the risk characterization, it should be indicated if absorption efficiency was considered and also

what exposure averaging periods are appropriate for comparison with the value."

NOTE: Although the toxicity values presented in the formal and condensed toxicity profiles were correct at the time they were produced, these values are subject to change. Users should refer to the RAGS Part A format for the currect toxicity values and information.

Tutorial

Select a Profile

Analyte	CAS Number	Formal Version	Condensed Version	RAGs, Part A Format
Acenaphthene	83329	Formal	Summary	RAGs A
Acetone	67641	Formal	Summary	RAGs A
Aluminum	7429905	Formal	Summary	RAGs A
Anthracene	120127	Formal	Summary	RAGs A
Antimony (metallic)	7440360	Formal	Summary	RAGs A
Aroclor-1254	11097691	Formal	Summary	RAGs A
Aroclor-1260	11096825	Formal	Summary	RAGs A
Arsenic	7440382	Formal	Summary	RAGs A
Asbestos	1332214	Formal	Summary	RAGs A
Barium	7440393	Formal	Summary	RAGs A
Benzo[a]pyrene	50328	Formal	Summary	RAGs A
Benz[a]anthracene	56553	Formal	Summary	RAGs A
Benzene	71432	Formal	Summary	RAGs A

Benzo[b]fluoranthene	205992	Formal	Summary	RAGs A
Benzo[k]fluoranthene	207089	Formal	Summary	RAGs A
Benzo[g,h,i]perylene	191242	Formal	Summary	RAGs A
Beryllium	7440417	Formal	Summary	RAGs A
Bis(2-ethylhexyl)phthalate	117817	Formal	Summary	RAGs A
Bromoform	75252	Formal	Summary	RAGs A
Cadmium	7440439	Formal	Summary	RAGs A
Carbon Tetrachloride	56235	Formal	Summary	RAGs A
Chlordane	57749	Formal	Summary	RAGs A
Chloroform	67663	Formal	Summary	RAGs A
Chromium	7440473	Formal	Summary	RAGs A
Chromium III	16065831			
Chromium VI	18540299			
Chrysene	218019	Formal	Summary	RAGs A
Copper	7440508	Formal	Summary	RAGs A
Cyanide	57125	Formal	Summary	RAGs A
Dibenz[a,h]anthracene	53703	Formal	Summary	RAGs A
Dichloroethylene, 1,1-	75354	Formal	Summary	RAGs A
1,4-Dichlorobenzene	106467	Formal	Summary	RAGs A
1,1-Dichloroethane	75343	Formal	Summary	RAGs A
1,2-Dichloroethane	107062	Formal	Summary	RAGs A
1,2-Dichloroethylene	540590	Formal	Summary	RAGs A
cis-1,2-Dichloroethylene	156592			

2,4-Dinitrotoluene	121142	Formal	Summary	RAGs A
2,6-Dinitrotoluene	606202	Formal	Summary	RAGs A
Ethylbenzene	100414	Formal	Summary	RAGs A
Fluoranthene	206440	Formal	Summary	RAGs A
Heptachlor	76448	Formal	Summary	RAGs A
Heptachlor Epoxide	1024573	Formal	Summary	RAGs A
Indeno[1,2,3-cd]pyrene	193395	Formal	Summary	RAGs A
Lead	7439921	Formal	Summary	RAGs A
Lithium	7439932	Formal	Summary	RAGs A
Manganese	7439965	Formal	Summary	RAGs A
Mercury	7439976	Formal	Summary	RAGs A
Methyl Isobutyl Ketone	108101	Formal	Summary	RAGs A
Methylene Chloride	75092	Formal	Summary	RAGs A
Methyl Mercury	2269926	Formal	Summary	RAGs A
Molybdenum	7439987	Formal	Summary	RAGs A
Naphthalene	91203	Formal	Summary	RAGs A
Nickel and Nickel Compounds	7440020	Formal	Summary	RAGs A
Nitrates	14797558	Formal	Summary	RAGs A
Nitrobenzene	98953	Formal	Summary	RAGs A
Pentachlorophenol	87865	Formal	Summary	RAGs A

Phenanthrene	85018	Formal	Summary	RAGs A
Pyrene	129000	Formal	Summary	RAGs A
Selenium	7782492	Formal	Summary	RAGs A
Silver	7440224	Formal	Summary	RAGs A
Strontium-90	10098972	Formal	Summary	RAGs A
Sulfate	14808798	Formal	Summary	RAGs A
1,1,2,2-tetrachloroethane	79345	Formal	Summary	RAGs A
Tetrachloroethylene	127184	Formal	Summary	RAGs A
Thallium	7440280	Formal	Summary	RAGs A
Toluene	108883	Formal	Summary	RAGs A
1,1,1-Trichloroethane	71556	Formal	Summary	RAGs A
1,1,2-Trichloroethane	79005	Formal	Summary	RAGs A
Trichloroethene	79016	Formal	Summary	RAGs A
Trinitrophenylmethylnitramine	479458	Formal	Summary	RAGs A
2,4,6-Trinitrotoluene	118967	Formal	Summary	RAGs A
Vanadium	7440622	Formal	Summary	RAGs A
Vinyl Chloride	75014	Formal	Summary	RAGs A
Xylene	1330207	Formal	Summary	RAGs A
Zinc	7440666	Formal	Summary	RAGs A

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Toxicity Profiles

Toxicity Summary for ASBESTOS

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

August 1995

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Prepared for OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM.

*Managed by Lockheed Martin Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400.

Asbestos (CAS No. 1332-21-4) is the generic name for a variety of naturally formed hydrated silicates containing metal cations such as sodium, magnesium, calcium, or iron. The two major groups of asbestos are serpentine and amphibole based on their physical/chemical properties. Chrysotile (CAS No. 12001-29-5) is the only asbestos in the serpentine group, whereas the amphibole group is represented by actinolite (CAS No. 13768-008), amosite (CAS No. 12172-73-5), anthophyllite (CAS No. 17068-78-9), crocidolite (CAS No. 12001-28-4), and tremolite (CAS No. 14567-73-8) (EPA 1984, ATSDR 1993). Asbestos fibers are chemically inert, or nearly so. They do not evaporate, dissolve, burn, or undergo significant reactions with other chemicals (ATSDR 1993).

Asbestos fibers can enter the body after inhalation or oral exposures. Fibers that are deposited in the lung may be removed from the lung by

mucociliary clearance or by macrophages, or they may be retained in the lungs (EPA 1980, 1984). Some ingested asbestos fibers penetrate the gastric mucosa, and a small percentage of the fibers are distributed to other tissues. Ingested fibers are mostly excreted in the feces (Cunningham et al. 1976).

Long-term feeding studies in rats and hamsters indicate that ingestion of high concentrations (1% in the diet or 500-800 mg/kg/day) of chrysotile, amosite, crocidolite, or tremolite does not cause systemic effects (NTP 1985; 1988a, b, c; 1990). Other studies reported some histological and biochemical alterations in cells of the gastrointestinal tract in rats receiving up to 50 mg/kg/day of chrysotile for 14-15 months (Jacobs et al. 1978a, b).

Numerous studies in humans have established that long-term inhalation of asbestos fibers causes chronic, progressive pneumoconiosis (asbestosis). The disease is common among occupational groups directly exposed to asbestos fibers, such as insulation workers, but also extends to those working near the application or removal of asbestos and family contacts of exposed workers (EPA 1980). Asbestosis results from a prolonged inflammatory response stimulated by the presence of fibers in the lungs and is characterized by fibrosis of the lung parenchyma, which usually becomes radiographically discernible 10 years after the first exposure (EPA 1985). The main clinical symptom is shortness of breath, often accompanied by rales and cough. In severe cases, impairment of respiratory function may ultimately result in death (ATSDR 1993). Because asbestos fibers are resistant to breakdown in the lungs, the inflammatory response triggered by the fibers is ongoing, even after exposure has ceased. It has been estimated that cumulative exposures of 17-75 fibers-year/mL would result in fibrotic lung lesions, and cumulative exposures of 3.5-300 fibers-year/mL would cause death in humans (ATSDR 1993).

Smoking has been shown to increase the risk of asbestosis (Schulz 1994). Fibrosis has been produced in laboratory animals following subchronic or chronic inhalation exposure to various forms of asbestos (Wagner 1963, Wagner et al. 1974, Donaldson et al. 1988). Some studies of workers with asbestos-related diseases indicate that the cellular immune system in such patients can be depressed (ATSDR 1993).

Dermal contact with asbestos may result in the formation of warts or corns (Alden and Howell 1944). An oral Reference Dose (RfD) or inhalation Reference Concentration (RfC) for asbestos has not been derived (EPA 1995).

Several epidemiologic studies suggest that high levels of asbestos in drinking water in certain geographic areas may cause gastrointestinal cancer in humans (Cooper et al. 1979, Conforti 1983, Kanarek 1983), whereas other studies failed to find a clear association between ingested

asbestos and cancer in humans (Harrington et al. 1978, Polissar et al. 1983). The evidence for carcinogenicity in orally exposed animals is also equivocal. A series of lifetime feeding studies with rats and Syrian golden hamsters with various forms of asbestos have yielded mostly negative results (NTP 1985; 1988a, b, c; 1990). An increased incidence of benign adenomatous polyps of the large intestine was observed in male rats exposed to 1% (500 mg/kg/day) intermediate range chrysotile (65% of fibers >10 m in length) in the diet (NTP 1985).

Numerous epidemiologic studies have documented an increased incidence of lung cancer and pleural and peritoneal mesothelioma (a tumor involving the lining of the abdomen and chest) as a result of asbestos exposure. All major types of commercial asbestos such as chrysotile, amosite, and crocidolite have been found to produce asbestos-related cancer among workers occupationally exposed in mining and milling, manufacturing, and using materials containing asbestos fibers (EPA 1980). Asbestos-related cancer has also been identified, although less frequently, in individuals who had worked near the application or removal of asbestos material, individuals residing in the vicinity of asbestos plants, and individuals who had lived in the household of an asbestos worker (IARC 1977, 1987).

For lung cancer, the magnitude of the carcinogenic risk appears to be a function of a number of factors, including the level and duration of exposure, the time since exposure occurred, the age at which exposure occurred, the smoking history of the exposed person, and the type and size distribution of asbestos fibers. A substantial latency period (10-30 years) has been observed between exposure to asbestos and the onset of lung cancer (ATSDR 1993). Many reports have documented cases of pleural and peritoneal mesotheliomas resulting from occupational and nonoccupational exposures to various types and mixtures of asbestos. It has been estimated that a third of the mesotheliomas occurring in the U.S. may be due to nonoccupational exposure (IARC 1977, 1987). Asbestos exposure and cigarette smoking act synergistically to produce dramatic increases in lung cancer compared with those from exposure to either agent alone (EPA 1984). The data for possible interactions between smoking and mesothelioma are not certain, but smoking does not appear to increase the risk for this cancer (Schulz 1994).

Reports of excess cancer incidences or mortality from cancers at other sites among workers exposed to asbestos are inconsistent. These cancers include cancers of the gastrointestinal system (esophagus, stomach, colon, bile duct, and rectum), laryngeal cancer, kidney cancer, ovarian cancer, and cancer affecting the lymphopoietic and hematopoietic systems (IARC 1977, Schulz 1994). However, the risk of these cancers appears to be significantly lower than those for lung cancer and mesothelioma in similarly exposed cohorts (Schulz 1994).

Several types of asbestos were shown to induce tumors in rats, including

mesotheliomas and lung adenomas/carcinomas following inhalation of 9.7-14.7 mg/m^3, 7 hours/day, 5 days/week for up to 24 months (Wagner et al. 1974). Intrapleural administration of asbestos induced mesotheliomas in rats and hamsters, and intraperitoneal administration induced abdominal tumors including mesotheliomas in rats and mice and abdominal tumors in hamsters (IARC 1977, 1987).

Based on EPA guidelines, asbestos was assigned to weight-of-evidence group A, human carcinogen (EPA 1995). Slope factors for oral or inhalation exposure are not available at this time. The inhalation unit risk for asbestos is 2.3E-1 [(fibers/mL)$^{-1}$] (EPA 1995).


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Toxicity Profiles

Toxicity Summary for ARSENIC

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

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Prepared for: OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM.

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400.

The toxicity of inorganic arsenic (As) depends on its valence state (-3, +3, or +5), and also on the physical and chemical properties of the compound in which it occurs. Trivalent (As^{+3}) compounds are generally more toxic than pentavalent (As^{+5}) compounds, and the more water soluble compounds are usually more toxic and more likely to have systemic effects than the less soluble compounds, which are more likely to cause chronic pulmonary effects if inhaled. One of the most toxic inorganic arsenic compounds is arsine gas (AsH_3). It should be noted that laboratory animals are generally less sensitive than humans to the toxic effects of inorganic arsenic. In addition, in rodents the critical effects appear to be immunosuppression and hepato-renal dysfunction, whereas in humans the skin, vascular system, and peripheral nervous system are the primary target organs.

Water soluble inorganic arsenic compounds are absorbed through the G.I. tract (>90%) and lungs; distributed primarily to the liver, kidney, lung, spleen, aorta, and skin; and excreted mainly in the urine at rates as high as 80% in 61 hr following oral dosing (U.S. EPA, 1984; ATSDR, 1989; Crecelius, 1977). Pentavalent arsenic is reduced to the trivalent form and then methylated in the liver to less toxic methylarsinic acids (ATSDR, 1989).

Symptoms of acute inorganic arsenic poisoning in humans are nausea, anorexia, vomiting, epigastric and abdominal pain, and diarrhea. Dermatitis (exfoliative erythroderma), muscle cramps, cardiac abnormalities, hepatotoxicity, bone marrow suppression and hematologic abnormalities (anemia), vascular lesions, and peripheral neuropathy (motor dysfunction, paresthesia) have also been reported (U.S. Air Force, 1990; ATSDR, 1989; Franzblau and Lilis, 1989; U.S. EPA, 1984; Armstrong et al., 1984; Hayes, 1982; Mizuta et al., 1956). Oral doses as low as 20-60 g/kg/day have been reported to cause toxic effects in some individuals (ATSDR, 1989). Severe exposures can result in acute encephalopathy, congestive heart failure, stupor, convulsions, paralysis, coma, and death. The acute lethal dose to humans has been estimated to be about 0.6 mg/kg/day (ATSDR, 1989). General symptoms of chronic arsenic poisoning in humans are weakness, general debility and lassitude, loss of appetite and energy, loss of hair, hoarseness of voice, loss of weight, and mental disorders (Hindmarsh and McCurdy, 1986). Primary target organs are the skin (hyperpigmentation and hyperkeratosis) [Terada et al. 1960; Tseng et al., 1968; Zaldivar 1974; Cebrian et al., 1983; Huang et al., 1985], nervous system (peripheral neuropathy) [Hindmarsh et al., 1977, 1986; Valentine et al., 1982; Heyman et al., 1956; Mizuta et al., 1956; Tay and Seah, 1975], and vascular system [Tseng et al., 1968; Borgano and Greiber, 1972; Salcedo et al., 1984; Wu et al., 1989; Hansen, 1990]. Anemia, leukopenia, hepatomegaly, and portal hypertension have also been reported (Terada et al., 1960; Viallet et al., 1972; Morris et al., 1974; Datta, 1976). In addition, possible reproductive effects include a high male to female birth ratio (Lyster, 1977).

In animals, acute oral exposures can cause gastrointestinal and neurological effects (Heywood and Sortwell, 1979). Oral LD_{50} values range from about 10 to 300 mg/kg (ASTDR, 1989; U.S. Air Force, 1990). Low subchronic doses can result in immunosuppression, (Blakely et al., 1980) and hepato-renal effects (Mahaffey et al., 1981; Brown et al., 1976; Woods and Fowler, 1977, 1978; Fowler and Woods, 1979; Fowler et al., 1979). Chronic exposures have also resulted in mild hyperkeratosis and bile duct enlargement with hyperplasia, focal necrosis, and fibrosis (Baroni et al., 1963; Byron et al., 1967). Reduction in litter size, high male/female birth ratios, and fetotoxicity without significant fetal abnormalities occur following oral exposures (Schroeder and Mitchener, 1971; Hood et al., 1977; Baxley et al., 1981); however, parenteral dosing has resulted in exencephaly, encephaloceles, skeletal defects, and

urogenital system abnormalities (Ferm and Carpenter, 1968; Hood and Bishop, 1972; Beaudoin, 1974; Burk and Beandoin, 1977).

The Reference Dose for chronic oral exposures, 0.0003 mg/kg/day, is based on a NOAEL of 0.0008 mg/kg/day and a LOAEL of 0.014 mg/kg/day for hyperpigmentation, keratosis, and possible vascular complications in a human population consuming arsenic-contaminated drinking water (U.S. EPA, 1991a). Because of uncertainties in the data, U.S. EPA (1991a) states that "strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value." The subchronic Reference Dose is the same as the chronic RfD, 0.0003 mg/kg/day (U.S. EPA, 1992).

Acute inhalation exposures to inorganic arsenic can damage mucous membranes, cause rhinitis, pharyngitis and laryngitis, and result in nasal septum perforation (U.S. EPA, 1984). Chronic inhalation exposures, as occurring in the workplace, can lead to rhino-pharyno-laryngitis, tracheobronchitis, (Lundgren, 1954); dermatitis, hyperpigmentation, and hyperkeratosis (Perry et al., 1948; Pinto and McGill, 1955); leukopenia (Kyle and Pease, 1965; Hine et al., 1977); peripheral nerve dysfunction as indicated by abnormal nerve conduction velocities (Feldman et al., 1979; Blom et al., 1985; Landau et al., 1977); and peripheral vascular disorders as indicated by Raynaud's syndrome and increased vasospastic reactivity in fingers exposed to low temperatures (Lagerkvist et al., 1986). Higher rates of cardiovascular disease have also been reported in some arsenic-exposed workers (Lee and Fraumeni, 1969; Axelson et al., 1978; Wingren and Axelson, 1985). Possible reproductive effects include a high frequency of spontaneous abortions and reduced birth weights (Nordström et al., 1978a,b). Arsine gas (AsH_3), at concentrations as low as 3-10 ppm for several hours, can cause toxic effects. Hemolysis, hemoglobinuria, jaundice, hemolytic anemia, and necrosis of the renal tubules have been reported in exposed workers (ACGIH, 1986; Fowler and Weissberg, 1974).

Animal studies have shown that inorganic arsenic, by intratracheal instillation, can cause pulmonary inflammation and hyperplasia (Webb et al., 1986, 1987), lung lesions (Pershagen et al., 1982), and immunosuppression (Hatch et al. (1985). Long-term inhalation exposures have resulted in altered conditioned reflexes and CNS damage (Rozenshstein, 1970). Reductions in fetal weight and in the number of live fetuses, and increases in fetal abnormalities due to retarded osteogenesis have been observed following inhalation exposures (Nagymajtenyi et al., 1985).

Subchronic and chronic RfCs for inorganic arsenic have not been derived.

Epidemiological studies have revealed an association between arsenic concentrations in drinking water and increased incidences of skin cancers (including squamous cell carcinomas and multiple basal cell carcinomas),

as well as cancers of the liver, bladder, respiratory and gastrointestinal tracts (U.S. EPA, 1987; IARC, 1987; Sommers et al., 1953; Reymann et al., 1978; Dobson et al., 1965; Chen et al., 1985, 1986). Occupational exposure studies have shown a clear correlation between exposure to arsenic and lung cancer mortality (IARC, 1987; U.S. EPA, 1991a). U.S. EPA (1991a) has placed inorganic arsenic in weight-of-evidence group A, human carcinogen. A drinking water unit risk of 5E-5$(ug/L)^{-1}$ has been proposed (U.S. EPA, 1991a); derived from drinking water unit risks for females and males that are equivalent to slope factors of 1.0E-3 $(ug/kg/day)^{-1}$ (females) and 2.0E-3 $(ug/kg/day)^{-1}$ (males) (U.S. EPA, 1987). For inhalation exposures, a unit risk of 4.3E-3 $(ug/m^3)^{-1}$ (U.S. EPA, 1991a) and a slope factor of 5.0E+1 $(mg/kg/day)^{-1}$ have been derived (U.S. EPA, 1992).


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Toxicity Profiles

Toxicity Summary for BARIUM

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

Prepared by A. A. Francis, M.S., D.A.B.T., and Carol S. Forsyth, Ph.D., Chemical Hazard Evaluation Group in the Biomedical and Environmental Information Analysis Section, Health Sciences Research Division, *.

Prepared for OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

The soluble salts of barium, an alkaline earth metal, are toxic in mammalian systems. They are absorbed rapidly from the gastrointestinal tract and are deposited in the muscles, lungs, and bone. Barium is excreted primarily in the feces.

At low doses, barium acts as a muscle stimulant and at higher doses affects the nervous system eventually leading to paralysis. Acute and subchronic oral doses of barium cause vomiting and diarrhea, followed by decreased heart rate and elevated blood pressure. Higher doses result in cardiac irregularities, weakness, tremors, anxiety, and dyspnea. A drop in serum potassium may account for some of the symptoms. Death can occur from cardiac and respiratory failure. Acute doses around 0.8 grams can be fatal to humans.

Subchronic and chronic oral or inhalation exposure primarily affects the cardiovascular system resulting in elevated blood pressure. A lowest-observed-adverse-effect level (LOAEL) of 0.51 mg barium/kg/day based on increased blood pressure was observed in chronic oral rat studies

(Perry et al. 1983), whereas human studies identified a no-observed-adverse-effect level (NOAEL) of 0.21 mg barium/kg/day (Wones et al. 1990, Brenniman and Levy 1984). The human data were used by the EPA to calculate a chronic and subchronic oral reference dose (RfD) of 0.07 mg/kg/day (EPA 1995a,b). In the Wones et al. study, human volunteers were given barium up to 10 mg/L in drinking water for 10 weeks. No clinically significant effects were observed. An epidemiological study was conducted by Brenniman and Levy in which human populations ingesting 2 to 10 mg/L of barium in drinking water were compared to a population ingesting 0 to 0.2 mg/L. No significant individual differences were seen; however, a significantly higher mortality rate from all combined cardiovascular diseases was observed with the higher barium level in the 65+ age group. The average barium concentration was 7.3 mg/L, which corresponds to a dose of 0.20 mg/kg/day. Confidence in the oral RfD is rated medium by the EPA.

Subchronic and chronic inhalation exposure of human populations to barium-containing dust can result in a benign pneumoconiosis called "baritosis." This condition is often accompanied by an elevated blood pressure but does not result in a change in pulmonary function. Exposure to an air concentration of 5.2 mg barium carbonate/m^3 for 4 hours/day for 6 months has been reported to result in elevated blood pressure and decreased body weight gain in rats (Tarasenko et al. 1977). Reproduction and developmental effects were also observed. Increased fetal mortality was seen after untreated females were mated with males exposed to 5.2 mg/m^3 of barium carbonate. Similar results were obtained with female rats treated with 13.4 mg barium carbonate/m^3. The NOAEL for developmental effects was 1.15 mg/m^3 (equivalent to 0.8 mg barium/m^3). An inhalation reference concentration (RfC) of 0.005 mg/m^3 for subchronic and 0.0005 mg/m^3 for chronic exposure was calculated by the EPA based on the NOAEL for developmental effects (EPA 1995a). These effects have not been substantiated in humans or other animal systems.

Barium has not been evaluated by the EPA for evidence of human carcinogenic potential (EPA 1995b).


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Toxicity Summary for BENZENE

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

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Benzene is absorbed via ingestion, inhalation, and skin application. Experimental data indicate that animals can absorb up to 95% of oral doses and that humans can absorb up to 80% of inhaled benzene (after 5 minutes of exposure) (Sabourin et al., 1987; Srobova et al., 1950). Humans may absorb benzene vapors through the skin as well as the lungs; of the total dose absorbed by the two routes, an estimated 22-36% enters the body through the skin (Susten, 1985).

Autopsy of a youth who died while sniffing benzene revealed that the chemical was distributed to the urine, stomach, bile, liver, kidney, abdominal fat, and brain (Winek and Collum, 1971). The depots for benzene and its metabolites in animals are similar to those in humans, and in addition, include the fetus and placenta, bone marrow, Zymbal gland, and oral and nasal cavities (Ghantous and Danielsson, 1986; Rickert et al., 1979; Low et al., 1989).

Numerous studies indicate that the metabolism of benzene is required for its toxicity (Kalf et al., 1987). The liver is the main site for the metabolism of benzene; the bone marrow, a minor site (ATSDR, 1992). Phenol, hydroquinone, catechol, and benzene oxide are the major metabolites (Kalf et al, 1987; Snyder, 1987). The metabolite(s) of benzene that are responsible for its toxicity have not been positively

identified, but likely candidates include muconaldehyde, quinones, and free radicals generated by oxidizing enzymes (Henderson et al., 1989; Snyder, 1987).

Benzene is eliminated either unchanged in expired air or as metabolites in the urine (ATSDR, 1992). The proportions of the administered dose excreted by each route and the half-times for excretion are dependent on route, dose, and duration of exposure.

Lethal oral doses of benzene are estimated to be 10 mL in humans; oral LD_{50} values for benzene in rats range from 0.93 to 5.96 g/kg (Cornish and Ryan, 1965; Withey and Hall, 1975). These data indicate that benzene is of low acute toxicity (O'Bryan and Ross, 1986).

Limited data show that nonlethal oral doses of benzene can impact the nervous, hematological, and immunological systems. Ingested benzene produces symptoms of neurotoxicity at acute doses of 2 mL for humans and 325 mg/kg for rats (Thienes and Haley, 1972; Clayton and Clayton, 1981; Cornish and Ryan, 1965). A four week exposure of mice to >=8 mg of benzene/kg/day in the drinking water induced the synthesis and catabolism of monoamine neurotransmitters and produced dose-related decreases in red-blood cell parameters and lymphocyte numbers (Hsieh et al., 1988b). Rats and mice that were treated with benzene by gavage for 103 weeks developed a dose-related lymphocytopenia (LOAEL, 25 mg/kg/day) and mice had hyperplasia of the bone marrow and lymphoid depletion of the splenic follicles and thymus (100 mg/kg/day) (Huff et al., 1989).

Inhalation of benzene vapor concentrations of 20,000 ppm for 5-10 minutes can be fatal to humans; death results from central nervous system depression (Clayton and Clayton, 1981). The estimated LC_{50} value for the rat is 13,700 ppm (Drew and Fouts, 1974).

As with orally administered benzene, the targets for nonlethal concentrations of inhaled benzene include the nervous, hematological, and immunological systems. Neurological symptoms in humans may appear at exposure concentrations of 700 ppm (Clayton and Clayton, 1981). In animals, 1 week of exposure to 300 ppm induced behavioral effects (Drew and Fouts, 1974), and one to four weeks of exposure to benzene concentrations ranging from 21-50 ppm suppressed the bone marrow (NOAEL, 10 ppm) (Cronkite et al., 1985; Toft et al., 1982), the cellular immune response (NOAEL, 10 ppm) (Rosenthal and Snyder, 1985), and the humoral immune response (LOAEL, 50 ppm) (Aoyama, 1986).

Subchronic and chronic exposures to benzene vapors induce a progressive depletion of the bone marrow and dysfunction of the hematopoietic system. Early symptoms of bone marrow depression include leukopenia, anemia or thrombocytopenia, or a combination of the three (Snyder,

1984). A group of workers exposed to benzene concentrations of 30 and 150 ppm for 4 months to 1 year had increased incidences of pancytopenia (Aksoy et al., 1971; Aksoy et al., 1972; Aksoy and Erdem, 1978). A group of patients who had been exposed to benzene concentrations of 150 to 650 ppm for 4 months to 15 years exhibited severe blood dyscrasias and eight of the 32 patients died with thrombocytopenic hemorrhage and infection (Aksoy et al., 1972). The human data are supported by animal data showing bone marrow suppression in mice and rats exposed to benzene concentrations ranging from 10 ppm for 24 weeks to 300 ppm for 13 weeks (Baarson et al., 1984; Ward et al., 1985).

Benzene may also have long-term effects on the central nervous system. Workers exposed to benzene for 0.5 to 4 years exhibited EEG changes and atypical sleep activity consistent with neurotoxicity (Kellerova, 1985). Others exposed to benzene concentrations of 210 ppm for 6-8 years had peripheral nerve damage (Baslo and Aksoy, 1982).

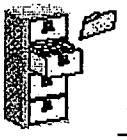
In humans, benzene crosses the placenta and is present in the cord blood in amounts equal to those in maternal blood (Dowty et al., 1976); however, studies of the effects of benzene on human reproduction and development have been confounded by the presence of other chemicals in the environment (USAF, 1989). Benzene does produce developmental effects (fetal toxicity, but not malformations) in the offspring of treated animals, mostly at maternally toxic doses (Nawrot and Staples, 1979; Seidenberg et al., 1986; Keller and Snyder, 1988).

Reference doses/concentrations for benzene have not been established. An oral risk assessment for benzene will be reviewed by an EPA work group and an inhalation risk assessment is currently under review (U.S. EPA, 1992a).

Benzene is carcinogenic in humans and animals by inhalation and in animals by the oral route of exposure. Occupational exposure to benzene has been associated mainly with increased incidences of acute myeloblastic or erythroblastic leukemias and chronic myeloid and lymphoid leukemias among workers (Aksoy, 1989). Workers at risk were exposed in one study to 8-hour TWA concentrations ranging from 10 to 100 ppm (Rinsky et al., 1981) and in another to 8-hour TWA concentrations ranging from <2 to >25 ppm (Ott et al., 1978). In a historical prospective mortality study of chemical workers, Yin et al. (1987) described a dose-response relationship between exposure to benzene and lymphatic and hematopoietic cancers, which adds strength to the association between exposure in the workplace and cancer development. Studies in animals have demonstrated an association between oral and inhalation exposure to benzene and the development of a variety of tumors, including lymphoma and carcinomas of the Zymbal gland, oral cavity, mammary gland, ovaries, lung, and skin (Huff et al., 1989; Maltoni et al., 1989). In one study C57Bl/BNL mice had increased incidences of leukemia, lymphoma, and solid tumors after exposure to

300 ppm for only 16 weeks (Cronkite et al., 1985; Cronkite, 1983).

Based on "several studies of increased incidence of nonlymphocytic leukemia from occupational exposure, increased incidence of neoplasia in rats and mice exposed by inhalation and gavage, and some supporting data", benzene has been placed in the EPA weight-of-evidence classification A, human carcinogen (U.S. EPA, 1991a). The oral and inhalation slope factors for benzene are 2.9E-2 $(mg/kg/day)^{-1}$ and the oral and inhalation unit risk values are 8.3E-7 and 8.3E-6, respectively, based on the studies of Ott et al. (1978), Rinsky et al. (1981), and Wong et al. (1983) (U.S. EPA, 1992a,b).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Toxicity Profiles

Toxicity Summary for CADMIUM

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

November 1991

Prepared by: Robert A. Young, Ph.D., D.A.B.T., Chemical Hazard Evaluation and Communication Group, Biomedical and Environmental Information Analysis Section, Health and Safety Research Division, *.

Prepared for OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM.

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400.

Cadmium is a naturally occurring metal that is used in various chemical forms in metallurgical and other industrial processes, and in the production of pigments. Environmental exposure can occur via the diet and drinking water (ATSDR, 1989).

Cadmium is absorbed more efficiently by the lungs (30 to 60%) than by the gastrointestinal tract, the latter being a saturable process (Nordberg et al., 1985). Cadmium is transported in the blood and widely distributed in the body but accumulates primarily in the liver and kidneys (Goyer, 1991). Cadmium burden (especially in the kidneys and liver) tends to increase in a linear fashion up to about 50 or 60 years of age after which the body burden remains somewhat constant. Metabolic transformations of cadmium are limited to its binding to protein and nonprotein sulfhydryl groups, and various macromolecules, such as metallothionein, which is

especially important in the kidneys and liver (ATSDR, 1989). Cadmium is excreted primarily in the urine.

Acute oral exposure to 20-30 g have caused fatalities in humans. Exposure to lower amounts may cause gastrointestinal irritation, vomiting, abdominal pain, and diarrhea (ATSDR, 1989). An asymptomatic period of one-half to one hour may precede the onset of clinical signs. Oral LD_{50} values in animals range from 63 to 1125 mg/kg, depending on the cadmium compound (USAF, 1990). Longer term exposure to cadmium primarily affects the kidneys, resulting in tubular proteinosis although other conditions such as "itai-itai" disease may involve the skeletal system. Cadmium involvement in hypertension is not fully understood (Goyer, 1991).

Inhalation exposure to cadmium and cadmium compounds may result in effects including headache, chest pains, muscular weakness, pulmonary edema, and death (USAF, 1990). The 1-minute and 10-minute lethal concentration of cadmium for humans has been estimated to be about 2,500 and 250 mg/m^3, respectively (Barrett et al., 1947; Beton et al., 1966). An 8-hour TWA (time-weighted-average) exposure level of 5 mg/m^3 has been estimated for lethal effects of inhalation exposure to cadmium, and exposure to 1 mg/m^3 is considered to be immediately dangerous to human health (Friberg, 1950). Renal toxicity (tubular proteinosis) may also result from inhalation exposure to cadmium (Goyer, 1991).

Chronic oral RfDs of 5E-4 and 1E-3 mg/kg/day have been established for cadmium exposure via drinking water and food, respectively (U.S. EPA, 1991). Both values reflect incorporation of an uncertainty factor of 10. The RfDs are based on an extensive data base regarding toxicokinetics and toxicity in both human and animals, the critical effect being renal tubular proteinuria. Confidence in the RfD and data base is high.

Inhalation RfC values are currently not available.

The target organ for cadmium toxicity via oral exposure is the kidney (Goyer, 1991). For inhalation exposure, both the lungs and kidneys are target organs for cadmium-induced toxicity (ATSDR, 1989; Goyer, 1991).

There is limited evidence from epidemiologic studies for cadmium-related respiratory tract cancer (ATSDR, 1989). An inhalation unit risk of 1.8E-3 $(\mu g/m^3)^{-1}$ and an inhalation slope factor of 6.1E+0 $(mg/kg/day)^{-1}$ are based on respiratory tract cancer associated with occupational exposure (U.S. EPA, 1985). Based on limited evidence from multiple occupational exposure studies and adequate animal data, cadmium is placed in weight-of-evidence group B1 - probable human carcinogen.

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Toxicity Profiles

Toxicity Summary for CHROMIUM

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

September 1992

Prepared by: Mary Lou Daugherty, M.S., Chemical Hazard Evaluation and Communication Group, Biomedical and Environmental Information Analysis Section, Health and Safety Research Division*, , Oak Ridge, Tennessee.

Prepared for: OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM.

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400.

Elemental chromium (Cr) does not occur in nature, but is present in ores, primarily chromite ($FeOCr_2O_3$) (Hamilton and Wetterhahn, 1988). Only two of the several oxidation states of chromium, Cr(III) and Cr(VI), are reviewed in this report based on their predominance and stability in the ambient environment and their toxicity in humans and animals.

Chromium plays a role in glucose and cholesterol metabolism and is thus an essential element to man and animals (Schroeder et al., 1962). Non-occupational exposure to the metal occurs via the ingestion of chromium-containing food and water, whereas occupational exposure occurs via inhalation (Langard, 1982; Pedersen, 1982). Workers in the chromate industry have been exposed to estimated chromium levels of 10-50 $\mu g/m^3$ for Cr(III) and 5-1000 $\mu g/m^3$ for Cr(VI); however,

improvements in the newer chrome-plating plants have reduced the Cr(VI) concentrations 10- to 40-fold (Stern, 1982).

Chromium(III) is poorly absorbed, regardless of the route of exposure, whereas chromium(VI) is more readily absorbed (Hamilton and Wetterhahn, 1988). Humans and animals localize chromium in the lung, liver, kidney, spleen, adrenals, plasma, bone marrow, and red blood cells (RBC) (Langard, 1982; ATSDR, 1989; Bragt and van Dura, 1983; Hamilton and Wetterhahn, 1988). There is no evidence that chromium is biotransformed, but Cr(VI) does undergo enzymatic reduction, resulting in the formation of reactive intermediates and Cr(III) (Hamilton and Wetterhahn, 1988). The main routes for the excretion of chromium are via the kidneys/urine and the bile/feces (Guthrie, 1982; Langard, 1982).

Animal studies show that Cr(VI) is generally more toxic than Cr(III), but neither oxidation state is very toxic by the oral route. In long-term studies, rats were not adversely affected by ~1.9 g/kg/day of chromic oxide [Cr(III)] (diet), 2.4 mg/kg/day of Cr(III) as chromic chloride (drinking water), or 2.4 mg/kg/day of Cr(VI) as potassium dichromate (drinking water) (Ivankovic and Preussmann, 1975; MacKenzie et al., 1958).

The respiratory and dermal toxicity of chromium are well-documented. Workers exposed to chromium have developed nasal irritation (at <0.01 mg/m^3, acute exposure), nasal ulcers, perforation of the nasal septum (at ~2 $\mu g/m^3$, subchronic or chronic exposure) (Hamilton and Wetterhahn, 1988; ATSDR, 1989; Lindberg and Hedenstierna, 1983) and hypersensitivity reactions and "chrome holes" of the skin (Pedersen, 1982; Burrows, 1983; U.S Air Force, 1990). Among the general population, contact dermatitis has been associated with the use of bleaches and detergents (Love, 1983).

Compounds of both Cr(VI) and Cr(III) have induced developmental effects in experimental animals that include neural tube defects, malformations, and fetal deaths (Iijima et al., 1983; Danielsson et al., 1982; Matsumoto et al., 1976).

The subchronic and chronic oral RfD value is 1 mg/kg/day for Cr(III). The subchronic and chronic oral RfD for Cr (VI) are 0.02 and 0.005 mg/kg/day, respectively (U.S. EPA, 1991a,b; 1992). The subchronic and chronic oral RfD values for Cr(VI) and Cr(III) are derived from no-observed-adverse-effect levels (NOAELs) of 1.47 g/kg Cr(III)/day and 25 ppm of potassium dichromate (Cr[VI]) in drinking water, respectively (Ivankovic and Preussmann, 1975; MacKenzie et al., 1958). The inhalation RfC values for both Cr(III) and Cr(VI) are currently under review by an EPA workgroup.

The inhalation of chromium compounds has been associated with the development of cancer in workers in the chromate industry. The relative risk for developing lung cancer has been calculated to be as much as 30

times that of controls (Hayes, 1982; Leonard and Lauwerys, 1980; Langard, 1983). There is also evidence for an increased risk of developing nasal, pharyngeal, and gastrointestinal carcinomas (Hamilton and Wetterhahn, 1988). Quantitative epidemiological data were obtained by Mancuso and Hueper (1951), who observed an increase in deaths (18.2%; $p<0.01$) from respiratory cancer among chromate workers compared with 1.2% deaths among controls. In a follow-up study, conducted when more than 50% of the cohort had died, the observed incidence for lung cancer deaths had increased to approximately 60% (Mancuso, 1975). The workers were exposed to 1-8 mg/m^3/year total chromium. Mancuso (1975) observed a dose response for total chromium exposure and attributed the lung cancer deaths to exposure to insoluble [Cr(III)], soluble [Cr(VI)], and total chromium. The results of inhalation studies in animals have been equivocal or negative (Nettesheim et al., 1971; Glaser et al, 1986; Baetjer et al., 1959; Steffee and Baetjer, 1965).

Based on sufficient evidence for humans and animals, Cr(VI) has been placed in the EPA weight-of-evidence classification A, human carcinogen (U.S. EPA, 1991a). For inhalation exposure, the unit risk value is 1.2E-2 $(\mu g/m^3)^{-1}$ and the slope factor is 4.1E+01 $(mg/kg/day)^{-1}$ (U.S. EPA, 1991a).


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Toxicity Profiles

Toxicity Summary for CYANIDE

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

February 1994

Prepared by Rosmarie A. Faust, Ph.D., Chemical Hazard Evaluation and Communication Group, Biomedical and Environmental Information Analysis Section, Health and Safety Research Division, *, Oak Ridge, Tennessee. Prepared for OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

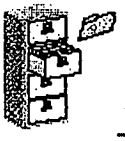
Cyanide most commonly occurs as hydrogen cyanide and its salts--sodium and potassium cyanide. Cyanides are both man-made and naturally occurring substances. They are found in several plant species as cyanogenic glycosides and are produced by certain bacteria, fungi, and algae. In very small amounts, cyanide is a necessary requirement in the human diet. Cyanides are released to the environment from industrial sources and car emissions (ATSDR, 1989).

Cyanides are readily absorbed by the inhalation, oral, and dermal routes of exposure. The central nervous system (CNS) is the primary target organ for cyanide toxicity. Neurotoxicity has been observed in humans and animals following ingestion and inhalation of cyanides. Cardiac and respiratory effects, possibly CNS-mediated, have also been reported. Short-term exposure to high concentrations produces almost immediate collapse, respiratory arrest, and death (Hartung, 1982; EPA, 1985). Symptoms resulting from occupational exposure to lower concentrations include breathing difficulties, nervousness, vertigo, headache, nausea,

vomiting, precordial pain, and electrocardiogram (EKG) abnormalities (Carmelo, 1955; El Ghawabi et al., 1975; Sandberg, 1967; Wuthrich, 1954). Thyroid toxicity has been observed in humans and animals following oral and inhalation exposure to cyanides (Philbrick et al., 1979; EPA, 1984). In animal studies, cyanides have produced fetotoxicity and teratogenic effects, including exencephaly, encephalocele, and rib abnormalities (Doherty et al., 1982; Frakes et al., 1986; Tewe and Maner, 1981b; Willhite, 1982).

Reference doses (RfDs) have been calculated for subchronic and chronic oral exposure to cyanide and several cyanide compounds (EPA, 1990a-e; 1991a-e). The values, derived from a single study, are based on a no-observed-adverse-effect level (NOAEL) of 10.8 mg/kg/day for cyanide in a 2-year dietary study with rats (Howard and Hanzal, 1955). The subchronic and chronic oral RfDs are 0.02 mg/kg/day for cyanide; 0.04 mg/kg/day for sodium cyanide, calcium cyanide, and cyanogen; 0.05 mg/kg/day for potassium cyanide, chlorine cyanide, and zinc cyanide; 0.1 mg/kg/day for silver cyanide; and 0.2 mg/kg/day for potassium silver cyanide. Data were insufficient to derive a reference concentration (RfC) for cyanide.

No suitable cancer bioassays or epidemiological studies are available to assess the carcinogenicity of cyanide. Therefore, EPA (1991b) has placed cyanide in weight-of-evidence group D, not classifiable as to human carcinogenicity.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Toxicity Profiles

Toxicity Summary for 1,2-DICHLOROETHANE

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

May 1994

Prepared by Dennis M. Opresko, Ph.D., Chemical Hazard Evaluation and Communication Program, Biomedical and Environmental Information Analysis Section, Health Sciences Research Division, *, Oak Ridge, Tennessee.

Prepared for OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM.

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under contract No. DE-AC05-84OR21400.

1,2-Dichloroethane is used primarily in the manufacture of vinyl chloride, as well as in the synthesis of tetrachloroethylene, trichloroethylene, 1,1,1-trichloroethane, vinylidene chloride, aziridines, and ethylenediamines (U.S. Air Force 1989, ATSDR 1992). It is added to gasoline as a lead-scavenging agent, and, in the past, has been used as a metal degreasing agent; a solvent; and a fumigant for grain, upholstery, and carpets. It has also been used in paints, coatings, adhesives, varnishes, finish removers, soaps, and scouring agents (U.S. Air Force 1989, ATSDR 1992).

1,2-Dichloroethane is expected to be highly mobile in most soils, and consequently, contamination of groundwater is possible. Adsorption to soil particles is low, particularly for soils with a low organic carbon

content. Volatilization from soils and surface waters may be an important transport process. Microbial biodegradation is not expected to be significant.

1,2-Dichloroethane is absorbed through the lungs, gastrointestinal system, and skin (ATSDR 1992). It is distributed throughout the body but may be concentrated in adipose tissue. The compound can also accumulate in breast milk (Urusova 1953) and may cross the placenta (Withey and Karpinski 1985, Vozovaya 1977). Metabolism of 1,2-dichloroethane most likely involves conjugation with glutathione (ATSDR 1992). Urinary metabolites are likely to include thiodiglycolic acid, chloroacetic acid, and N-acetyl-S-carboxymethyl-L-cysteine (NTP 1991). Excretion occurs primarily through elimination of soluble urinary metabolites (Reitz et al. 1982, Spreafico et al. 1980).

Bronchitis, hemorrhagic gastritis and colitis, hepatocellular damage, renal tubular necrosis, central nervous system depression, and histopathological changes in the brain have been reported in cases of acute oral poisoning of humans (ATSDR 1992, NIOSH 1976). Animal data indicate that short-term exposures may produce immune system deficiencies (Munson et al. 1982), and subchronic or chronic oral exposures may affect the liver or kidney (NTP 1991, Alumot et al. 1976). Subchronic or chronic oral reference doses for 1,2-dichloroethane have not been adopted by the United States Environmental Protection Agency (EPA) (EPA 1993a); however, a provisional reference dose (RfD) of 0.03 mg/kg/day has been calculated by the Superfund Health Risk Technical Support Center (EPA, 1994) from a no-observed-adverse-effects level (NOAEL) of 26 mg/kg/day for rats tested in a subchronic gavage study (NTP 1991). Use of this value in risk assessment reports for specific sites must be approved by the Support Center.

Acute inhalation exposures to 1,2-dichloroethane (75-125 ppm) can result in irritation of the eyes, nose and throat, dizziness, nausea, vomiting, increasing stupor, cyanosis, rapid pulse, delirium, anesthesia, partial paralysis, loss of tactile sense, degenerative changes in the myocardium, abnormal EEG, liver and kidney damage, pulmonary edema, and hemorrhages throughout the body (NIOSH 1976, CEC 1986, ATSDR 1992, Nouchi et al. 1984). Short-term exposures to animals have resulted in central nervous system depression (inactivity or stupor, tremors, uncertain gait, narcosis); pulmonary congestion; renal tubular degeneration; fatty degeneration of the liver and, less commonly, necrosis and hemorrhage of the adrenal cortex; chronic splenitis; fatty infiltration of the myocardium; and immuno-deficiency (Spencer et al. 1951, Heppel et al. 1946, Storer et al. 1984, Sherwood et al. 1987). Chronic occupational exposure to 1,2-dichloroethane may result in central nervous systems effects including irritability, sleeplessness, and decreased heart rate; loss of appetite; nausea; vomiting; epigastric pain, as well as irritation of the mucous membranes; and liver and kidney impairment (NIOSH 1976). Subchronic or chronic inhalation exposures to animals

resulted in pathological lesions in the kidney, liver, heart, lungs, and testes (Heppel et al. 1946, Spencer et al. 1951, Cheever et al. 1990). A subchronic or chronic inhalation reference concentration for 1,2-dichloroethane has not been adopted and verified by EPA (EPA 1993a); however, a provisional RfC of 0.005 mg/m^3 has been calculated by the Superfund Health Risk Technical Support Center (EPA 1994) from a LOAEL (gastrointestinal disturbances and liver and gallbladder disease) of 10 mg/m^3 for occupationally exposed workers (Kozik 1957). Use of this value in risk assessment reports for specific sites must be approved by the Support Center.

1,2-Dichloroethane is classified by EPA in Group B2 as a probable human carcinogen by both the oral and inhalation exposure routes, based on evidence for the induction of several types of tumors in rats and mice. Male rats treated by gavage with 1,2-dichloroethane exhibited increased incidences of fibromas of the subcutaneous tissue; hemangiosarcomas of the spleen, liver, pancreas, and adrenal gland; and squamous-cell carcinomas of the forestomach. Female rats treated by gavage developed mammary adenocarcinomas. Increased incidences of hepatocellular carcinomas and pulmonary adenomas were observed in male mice treated by gavage, and increased incidences of mammary adenocarcinomas, pulmonary adenocarcinomas, and endometrial polyps and sarcomas were observed in female mice (NCI 1978). Mice treated by topical application of 1,2-dichloroethane exhibited an increased incidence of lung papillomas (Van Duuren et al., 1979). The oral slope factor for 1,2-dichloroethane is 9.1E-2 $(ug/kg/day)^{-1}$, and the drinking water unit risk is 2.6E-6 $(ug/L)^{-1}$. The inhalation slope factor is 9.1E-2 $(ug/kg/day)^{-1}$, and the inhalation unit risk is 2.6E-5 $(ug/m^3)^{-1}$ (EPA 1993a, 1993b).


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1,2-dichloropropane is unclassifiable as to human carcinogenicity.

Is there a medical test to show whether I've been exposed to 1,2-dichloropropane?

Urine and blood tests can be used to find out if you have been exposed to 1,2-dichloropropane. Levels measured in the urine can be used to predict the levels in the air. These tests cannot predict whether you will suffer harmful effects. Because special equipment is needed, these tests are not usually done in the doctor's office.

Has the federal government made recommendations to protect human health?

The EPA has set a Maximum Contaminant Level (MCL) of 0.005 parts per million (0.005 ppm) for 1,2-dichloropropane in drinking water. The EPA recommends that the level of 1,2-dichloropropane in lakes and streams should be limited to 0.52 parts per billion (0.52 ppb) to prevent possible human health effects from drinking contaminated water or eating contaminated fish. Any release to the environment greater than 1,000 pounds of 1,2-dichloropropane must be reported to the EPA.

The Occupational Safety and Health Administration (OSHA) has set a workplace air concentration limit of 75 ppm over an 8-hour workday, 40-hour workweek.

The federal recommendations have been updated as of July 1999.

Glossary

Anemia: A decreased ability of the blood to transport oxygen.

CAS: Chemical Abstracts Service.

Carcinogenicity: Ability to cause cancer.

Evaporate: To change into a vapor or a gas.

Long-term: Lasting one year or longer.

National Priorities List: A list of the nation's worst hazardous waste sites.

ppb: Parts per billion.

ppm: Parts per million.

Short-term: Lasting 14 days or less.

Tumor: An abnormal mass of tissue.

Source of Information

Agency for Toxic Substances and Disease Registry (ATSDR). 1989. Toxicological profile for 1,2-dichloropropane. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Animal testing is sometimes necessary to find out how toxic substances might harm people and how to treat people who have been exposed. Laws today protect the welfare of research animals and scientists must follow strict guidelines.

Where can I get more information?

ATSDR can tell you where to find occupational and environmental health clinics. Their specialists can recognize, evaluate, and treat illnesses resulting from exposure to hazardous substances. You can also contact your community or state health or environmental quality department if you have any more questions or concerns.

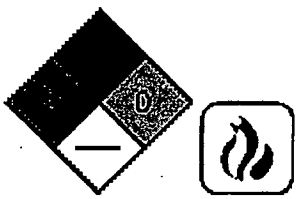
For more information, contact:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333
Phone: 1-888-422-8737
FAX: (404)498-0057

External safety and chemistry information (please see our disclaimer):

1,2-Dichloropropane
$C_3H_6Cl_2$

Stereo Image
MDL Molfile



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Toxicity Profiles

Toxicity Summary for LEAD

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

December 1994

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Prepared for OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM.

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under contract No. DE-AC05-84OR21400.

Lead occurs naturally as a sulfide in galena. It is a soft, bluish-white, silvery gray, malleable metal with a melting point of 327.5C. Elemental lead reacts with hot boiling acids and is attacked by pure water. The solubility of lead salts in water varies from insoluble to soluble depending on the type of salt (IARC, 1980; Goyer, 1988; Budavari et al., 1989).

Lead is a natural element that is persistent in water and soil. Most of the lead in environmental media is of anthropogenic sources. The mean concentration is 3.9 ug/L in surface water and 0.005 ug/L in sea water. River sediments contain about 20,000 ug/g and coastal sediments about 100,000 ug/g. Soil content varies with the location, ranging up to 30 ug/g in rural areas, 3000 ug/g in urban areas, and 20,000 ug/g near point sources. Human exposure occurs primarily through diet, air, drinking water, and ingestion of dirt and paint chips (EPA, 1989; ATSDR, 1993).

The efficiency of lead absorption depends on the route of exposure, age, and nutritional status. Adult humans absorb about 10-15% of ingested lead, whereas children may absorb up to 50%, depending on whether lead is in the diet, dirt, or paint chips. More than 90% of lead particles deposited in the respiratory tract are absorbed into systemic circulation. Inorganic lead is not efficiently absorbed through the skin; consequently, this route does not contribute considerably to the total body lead burden (EPA, 1986a).

Lead absorbed into the body is distributed to three major compartments: blood, soft tissue, and bone. The largest compartment is the bone, which contains about 95% of the total body lead burden in adults and about 73% in children. The half-life of bone lead is more than 20 years. The concentration of blood lead changes rapidly with exposure, and its half-life of only 25-28 days is considerably shorter than that of bone lead. Blood lead is in equilibrium with lead in bone and soft tissue. The soft tissues that take up lead are liver, kidneys, brain, and muscle. Lead is not metabolized in the body, but it may be conjugated with glutathione and excreted primarily in the urine (EPA, 1986a,c; ATSDR, 1993). Exposure to lead is evidenced by elevated blood lead levels.

The systemic toxic effects of lead in humans have been well-documented by the EPA (EPA, 1986a-e, 1989a, 1990) and ATSDR (1993), who extensively reviewed and evaluated data reported in the literature up to 1991. The evidence shows that lead is a multitargeted toxicant, causing effects in the gastrointestinal tract, hematopoietic system, cardiovascular system, central and peripheral nervous systems, kidneys, immune system, and reproductive system. Overt symptoms of subencephalopathic central nervous system (CNS) effects and peripheral nerve damage occur at blood lead levels of 40-60 ug/dL, and nonovert symptoms, such as peripheral nerve dysfunction, occur at levels of 30-50 ug/dL in adults; no clear threshold is evident. Cognitive and neuropsychological deficits are not usually the focus of studies in adults, but there is some evidence of neuropsychological impairment (Ehle and McKee, 1990) and cognitive deficits in lead workers with blood levels of 41-80 ug/dL (Stollery et al., 1993).

Although similar effects occur in adults and children, children are more sensitive to lead exposure than are adults. Irreversible brain damage occurs at blood lead levels greater than or equal to 100 ug/dL in adults and at 80-100 ug/dL in children; death can occur at the same blood levels in children. Children who survive these high levels of exposure suffer permanent severe mental retardation.

As discussed previously, neuropsychological impairment and cognitive (IQ) deficits are sensitive indicators of lead exposure; both neuropsychological impairment and IQ deficits have been the subject of cross-sectional and longitudinal studies in children. One of the early

studies reported IQ score deficits of four points at blood lead levels of 30-50 ug/dL and one to two points at levels of 15-30 ug/dL among 75 black children of low socioeconomic status (Schroeder and Hawk, 1986).

Very detailed longitudinal studies have been conducted on children (starting at the time of birth) living in Port Pirie, Australia (Vimpani et al., 1985, 1989; McMichael et al., 1988; Wigg et al., 1988; Baghurst et al., 1992a,b), Cincinnati, Ohio (Dietrich et al., 1986, 1991, 1992, 1993), and Boston, Massachusetts (Bellinger et al., 1984, 1987, 1990, 1992; Stiles and Bellinger 1993). Various measures of cognitive performance have been assessed in these children. Studies of the Port Pirie children up to 7 years of age revealed IQ deficits in 2-year-old children of 1.6 points for each 10-ug/dL increase in blood lead, deficits of 7.2 points in 4-year-old children, and deficits of 4.4 to 5.3 points in 7-year-old children as blood lead increased from 10-30 ug/dL. No significant neurobehavioral deficits were noted for children, 5 years or younger, who lived in the Cincinnati, Ohio, area. In 6.5-year-old children, performance IQ was reduced by 7 points in children whose lifetime blood level exceeded 20 ug/dL.

Children living in the Boston, Massachusetts, area have been studied up to the age of 10 years. Cognitive performance scores were negatively correlated with blood lead in the younger children in the high lead group (greater than or equal to 10 ug/dL), and improvements were noted in some children at 57 months as their blood lead levels became lower. However, measures of IQ and academic performance in 10-year-old children showed a 5.8-point deficit in IQ and an 8.9-point deficit in academic performance as blood lead increased by 10 ug/dL within the range of 1-25 ug/dL. Because of the large database on subclinical neurotoxic effects of lead in children, only a few of the studies have been included. However, EPA (EPA, 1986a, 1990) concluded that there is no clear threshold for neurotoxic effects of lead in children.

In adults, the cardiovascular system is a very sensitive target for lead. Hypertension (elevated blood pressure) is linked to lead exposure in occupationally exposed subjects and in the general population. Three large population-based studies have been conducted to study the relationship between blood lead levels and high blood pressure. The British Regional Heart Study (BRHS) (Popcock et al., 1984), the NHANES II study (Harlan et al., 1985; Pirkle et al., 1985; Landis and Flegal, 1988; Schwartz, 1990; EPA, 1990), and Welsh Heart Programme (Ellwood et al., 1988a,b) comprise the major studies for the general population. The BRHS study showed that systolic pressure greater than 160 mm Hg and diastolic pressure greater than 100 mm Hg were associated with blood lead levels greater than 37 ug/dL (Popcock et al., 1984). An analysis of 9933 subjects in the NHANES study showed positive correlations between blood pressure and blood lead among 12-74-year-old males but not females (Harlan et al., 1985; Landis and Flegal et al., 1988), 40-59-year-old white males with blood levels ranging

from 7-34 ug/dL (Pirkle et al., 1985), and males and females greater than 20 years old (Schwartz, 1991). In addition, left ventricular hypertrophy was also positively associated with blood lead (Schwartz, 1991). The Welsh study did not show an association among men and women with blood lead of 12.4 and 9.6 ug/dL, respectively (Ellwood et al., 1988a,b). Other smaller studies showed both positive and negative results. The EPA (EPA, 1990) concluded that increased blood pressure is positively correlated with blood lead levels in middle-aged men, possibly at concentrations as low as 7 ug/dL. In addition, the EPA estimated that systolic pressure is increased by 1.5-3.0 mm Hg in males and 1.0-2.0 mm Hg in females for every doubling of blood lead concentration.

The hematopoietic system is a target for lead as evidenced by frank anemia occurring at blood lead levels of 80 ug/dL in adults and 70 ug/dL in children. The anemia is due primarily to reduced heme synthesis, which is observed in adults having blood levels of 50 ug/dL and in children having blood levels of 40 ug/dL. Reduced heme synthesis is caused by inhibition of key enzymes involved in the synthesis of heme. Inhibition of erythrocyte -aminolevulinic acid dehydrase (ALAD) activity (catalyzes formation of porphobilinogen from -aminolevulinic acid) has been detected in adults and children having blood levels of less than 10 ug/dL. ALAD activity is the most sensitive measure of lead exposure, but erythrocyte zinc protoporphyrin is the most reliable indicator of lead exposure because it is a measure of the toxicologically active fraction of bone lead. The activity of another erythrocyte enzyme, pyrimidine-5-nucleotidase, is also inhibited by lead exposure. Inhibition has been observed at levels below 5 ug/dL; no clear threshold is evident.

Other organs or systems affected by exposure to lead are the kidneys, immune system, reproductive system, gastrointestinal tract, and liver. These effects usually occur at high blood levels, or the blood levels at which they occur have not been sufficiently documented.

The EPA has not developed an RfD for lead because it appears that lead is a nonthreshold toxicant, and it is not appropriate to develop RfDs for these types of toxicants. Instead the EPA has developed the Integrated Exposure Uptake Biokenetic Model to estimate the percentage of the population of children up to 6 years of age with blood lead levels above a critical value, 10 ug/dL. The model determines the contribution of lead intake from multimedia sources (diet, soil and dirt, air, and drinking water) on the concentration of lead in the blood. Site-specific concentrations of lead in various media are used when available; otherwise default values are assumed. The EPA has established a screening level of 400 ppm (ug/g) for lead in soil (EPA, 1994a).

Inorganic lead and lead compounds have been evaluated for carcinogenicity by the EPA (EPA, 1989, 1993). The data from human studies are inadequate for evaluating the potential carcinogenicity of lead. Data from animal studies, however, are sufficient based on numerous

studies showing that lead induces renal tumors in experimental animals. A few studies have shown evidence for induction of tumors at other sites (cerebral gliomas; testicular, adrenal, prostate, pituitary, and thyroid tumors). A slope factor was not derived for inorganic lead or lead compounds.

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Selenium occurs in several valence states: -2 (hydrogen selenide, sodium selenide, dimethyl selenium, trimethyl selenium, and selenoamino acids such as selenomethionine; 0 (elemental selenium); +4 (selenium dioxide, selenious acid, and sodium selenite); and +6 (selenic acid and sodium selenate). Toxicity of selenium varies with valence state and water solubility of the compound in which it occurs. The latter can affect gastrointestinal absorption rates.

Gastrointestinal absorption in animals and humans for various selenium compounds ranges from about 44% to 95% of the ingested dose (Thomson and Stewart, 1974; Bopp et al., 1982; Thomson, 1974). Respiratory tract absorption rates of 97% and 94% for aerosols of selenious acid have been reported for dogs and rats, respectively (Weissman et al., 1983; Medinsky et al., 1981). Selenium is found in all tissues of the body; highest concentrations occur in the kidney, liver, spleen, and pancreas (Schroeder and Mitchener, 1971a; Schroeder and Mitchener, 1972; Jacobs and Forst, 1981a; Julius et al., 1983; Shamberger, 1984; Echevarria et al., 1988). Excretion is primarily via the urine (0-15 g/L); however, excretory products can also be found in the feces, sweat, and in expired air.

In humans, acute oral exposures can result in excessive salivation, garlic odor to the breath, shallow breathing, diarrhea, pulmonary edema, and death (Civil and McDonald, 1978; Carter, 1966; Koppel et al., 1986). Other reported signs and symptoms of acute selenosis include tachycardia, nausea, vomiting, abdominal pain, abnormal liver function, muscle aches and pains, irritability, chills, and tremors. Acute toxic effects observed in animals include pulmonary congestion, hemorrhages and edema, convulsions, altered blood chemistry (increased hemoglobin and hematocrit); liver congestion; and congestion and hemorrhage of the kidneys (Smith et al., 1937; Anderson and Moxon, 1942; Hopper et al., 1985).

General signs and symptoms of chronic selenosis in humans include loss of hair and nails, acropachia (clubbing of the fingers), skin lesions (redness, swelling, blistering, and ulcerations), tooth decay (mottling, erosion and pitting), and nervous system abnormalities attributed to polyneuritis (peripheral anesthesia, acroparaethesia, pain in the extremities, hyperreflexia of the tendon, numbness, convulsions, paralysis, motor disturbances, and hemiplegia). In domesticated animals, subchronic and chronic oral exposures can result in loss of hair, malformed hooves, rough hair coat, and nervous system abnormalities (impaired vision and paralysis). Damage to the liver and kidneys and impaired immune responses have been reported to occur in rodents following subchronic and/or chronic oral exposures (Ganther and Baumann, 1962; Beems and van Beek, 1985; NCI, 1980a; Tinsley et al., 1967; Harr et al., 1967; Schroeder, 1967).

Selenium is teratogenic in birds and possibly also in domesticated animals (pigs, sheep, and cattle), but evidence of teratogenicity in humans and laboratory animals is lacking (ASTDR, 1989). However, adverse reproductive and developmental effects (decreased rates of conception, increased rates of fetal resorption, and reduced fetal body weights) have been reported for domesticated and laboratory animals (Harr and Muth, 1972: Wahlstrom and Olson, 1959; Schroeder and Mitchener, 1971b).

The Reference Dose (RfD) for chronic oral exposures is 0.005 mg/kg/day for both selenium and selenious acid (U.S. EPA, 1992a, 1992b). The subchronic RfDs for these compounds are the same as the chronic RfDs (U.S. EPA, 1992c).

In humans, inhalation of selenium or selenium compounds primarily affects the respiratory system. Dusts of elemental selenium and selenium dioxide can cause irritation of the skin and mucous membranes of the nose and throat, coughing, nosebleed, loss of sense of smell, dyspnea, bronchial spasms, bronchitis, and chemical pneumonia (Clinton, 1947; Hamilton, 1949). Other signs and symptoms following acute inhalation exposures include lacrimation, irritation and redness of the eyes, gastrointestinal distress (nausea and vomiting), depressed blood pressure, elevated pulse rate, headaches, dizziness, and malaise (ATSDR, 1989). In animals, acute inhalation exposures also result in severe respiratory effects including edema, hemorrhage, and interstitial pneumonitis (Hall et al., 1951; Dudley and Miller, 1937) as well as in splenic damage (congestion, fissuring red pulp, and increased polymorphonuclear leukocytes) and liver congestion and mild central atrophy (Hall et al., 1951). Information on toxicity of selenium in humans and animals following chronic inhalation exposures is not available, and subchronic and chronic inhalation Reference Concentrations have not been derived.

Epidemiologic studies in humans havation between chronic oral exposures to selenium and an increased incidence of death due to neoplasms. Some studies have indicated that selenium may have anti-neoplastic properties (see Whanger, 1983; Hocman, 1988). In studies on laboratory animals, selenites or selenates have not been found to be carcinogenic; however, selenium sulfide produced a significant increase in the incidence of hepatocellular carcinomas in male and female rats and in female mice and a significant increase in alveolar/bronchiolar carcinomas and adenomas in female mice following chronic oral exposures (NCI, 1980c). EPA has placed selenium and selenious acid in Group D, not classifiable as to carcinogenicity in humans (U.S. EPA, 1992a and 1992b), while selenium sulfide is placed in Group B2, probable human carcinogen (U.S. EPA, 1992d). Quantitative data are, however, insufficient to derive a slope factor for selenium sulfide. Pertinent data regarding the potential carcinogenicity of selenium by the inhalation route in humans or animals were not located in the available literature.

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Toxicity Profiles

Toxicity Summary for TOLUENE

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

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Prepared for: Oak Ridge Reservation Environmental Restoration Program.

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Toluene is a colorless liquid widely used as raw material in the production of organic compounds and as a solvent (EPA, 1990). It is readily absorbed from the gastrointestinal and respiratory tracts and, to a lesser degree, through the skin. Toluene is distributed throughout the body, with accumulation in tissues with high lipid content. It is metabolized in the liver, primarily to hippuric acid and benzoyl glucuronide, compounds that are rapidly excreted in the urine (EPA, 1990; ATSDR, 1989).

In humans and animals, the primary effect associated with inhalation exposure to toluene is central nervous system (CNS) depression. Short-term exposure of humans to 100-1500 ppm has elicited CNS effects such as fatigue, confusion, incoordination, and impairments in reaction time, perception, and motor control and function (NTP, 1990). Exposure to concentrations ranging from 10,000-30,000 ppm has resulted in

narcosis and deaths (WHO, 1985). Prolonged abuse of toluene or solvent mixtures containing toluene has led to permanent CNS effects. Exposure to high concentrations of toluene (1500 ppm) has produced hearing loss in rats (Pryor et al., 1984). Hepatomegaly and impaired liver and kidney function have been reported in some humans chronically exposed to toluene (Askergren, 1984; Szilard et al., 1978; Greenburg et al., 1942). Toluene vapors may cause eye irritation (Andersen et al., 1983), and prolonged or repeated dermal contact may produce drying of skin and dermatitis (ATSDR, 1989; NIOSH, 1973).

In experimental animals, subchronic inhalation exposure to 2500 ppm toluene resulted in increased liver and kidney weights (rats and mice), increased heart weights (rats), increased lung weights, and centrilobular hypertrophy of the liver (mice) (NTP, 1990). Chronic inhalation exposure to 600 or 1200 ppm for 2 years produced degeneration of olfactory and respiratory epithelia of rats and minimal hyperplasia of bronchial epithelia in mice (NTP, 1990).

Subchronic oral administration of toluene at doses ranging from 312 to 5000 mg/kg/day produced clinical signs of neurotoxicity at 2500 mg/kg in rats and mice. Other effects observed at higher doses in rats included increased relative liver, kidney, and heart weights (females only) and necrosis of the brain and hemorrhage of the urinary bladder (NTP, 1990).

Equivocal evidence shows that exposure to toluene in utero causes an increased risk of CNS abnormalities and developmental delay in humans (Goodwin, 1988; Hersh et al., 1985; Holmberg, 1979). Animal studies, in which toluene was administered by inhalation, showed that exposure results in fetotoxicity and delayed skeletal development but does not cause internal or external malformations in rats (Courtney et al., 1986; Litton Bionetics, 1978). An oral study noted an increased incidence of embryonic deaths, cleft palate, and maternal toxicity in mice administered 1 mL/kg toluene during gestation (Nawrot and Staples, 1979).

An oral reference dose (RfD) of 2 mg/kg/day for subchronic exposure (EPA, 1993) and 0.2 mg/kg/day for chronic exposure (EPA, 1992) to toluene was calculated based on a no-observed-adverse-effect level (NOAEL) of 223 mg/kg/day and a lowest-observed-adverse-effect level (LOAEL) of 446 mg/kg/day from a 13-week subchronic gavage study in rats (NTP, 1990). Increased liver and kidney weights in males were identified as the critical effects. A subchronic (EPA, 1993) and chronic inhalation reference concentration (RfC) of 0.4 mg/m^3 (EPA, 1992) was calculated based on results of a battery of neurological tests with occupationally exposed female subjects (Foo et al., 1990).

An increased incidence of hemolymphoreticular neoplasms was reported in rats exposed to 500 mg/kg of toluene by gavage for 2 years (Maltoni et al., 1985); however, results from two long-term inhalation studies (NTP, 1990; Gibson and Hardisty, 1983) indicate that toluene is not

carcinogenic at concentrations up to 1200 ppm. Based on U.S. Environmental Protection Agency (EPA) guidelines, toluene was assigned to weight-of-evidence group D, not classifiable as to human carcinogenicity (EPA, 1992).


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Toxicity Profiles

Toxicity Summary for 1,1,2,2-TETRACHLOROETHANE

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

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Prepared for OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

1,1,2,2-Tetrachloroethane (CAS No. 79-34-5) is a two-carbon chain molecule with two chlorine atoms on each carbon atom. Uses of 1,1,2,2-tetrachloroethane have been as a chemical intermediate, industrial solvent, and extractant. 1,1,2,2-Tetrachloroethane was found on at least 278 of the hazardous waste sites on the United States Environmental Protection Agency's National Priorities List. Chemical degradation occurs by the loss of chlorine atoms, and the half-life of 1,1,2,2-tetrachloroethane in air is about 2 months and in groundwater 1 to 3 months. Bioaccumulation of 1,1,2,2-tetrachloroethane in fish and other aquatic organisms is not expected to be significant (ATSDR;1994).

Two human studies suggested that between 50 and 97% of inspired 1,1,2,2-tetrachloroethane was retained (Lehman and Schmidt-Kehl 1936, Morgan et al. 1970). Mouse and rat gavage studies indicated that 100% of 1,1,2,2-tetrachloroethane was absorbed (Dow Chemical Company 1988). Animal metabolites were trichloroethane, trichloroacetic acid, dichloroacetic acid, glyoxylic acid, and oxalic acid (Ikeda and Ohtsuji 1972, Mitoma et al. 1985, Yllner 1971). Vinyl chloride is another possible

metabolite (Hallen et al. 1986). Human and animal studies indicate that the majority of 1,1,2,2-tetrachloroethane is metabolized (ATSDR 1994). Ten percent or less of the parent compound is exhaled in humans and animals.

Humans acutely exposed by the oral route had clinical signs inclusive of pulmonary congestion and edema (Hepple 1927, Mant 1953), lung collapse (Mant 1953) shallow breathing during unconsciousness, low blood pressure, a faint pulse (Sherman 1953, Ward 1955), and epicardial and endocardial anoxic hemorrhage (Mant 1953). Acute inhalation exposure studies of humans to concentrations ranging from 116 to 262 ppm for 10 to 30 minutes resulted in mucosal irritation, nausea and vomiting, eye mucosal irritation, and dizziness (Lehman and Schmidt-Kehl 1936).

A man died after cleaning a spill of 1,1,2,2-tetrachloroethane with his bare hands. His spleen was found to be enlarged with nodular areas on the surface (Coyer 1944). Chronic exposures in humans have resulted in reports of headache, tremors, dizziness, numbness, drowsiness, gastrointestinal distress, liver destruction, fatty degeneration in the liver (Hamilton 1917, Koelsch 1915, Lobo-Mendonca 1963, Minot and Smith 1921, Willcox et al. 1915). Jaundice and enlarged livers have also been reported in exposed workers (Coyer 1944, Horiguchi et al. 1964, Jeney et al. 1957, Koelsch;1915).

Acute oral lethal concentrations in rats range from 200 to 330 mg/kg (ATSDR 1994). Centrilobular swelling was observed in mice after an oral dose of 75 mg/kg/day given for 4 days (Dow Chemical Company 1988). Body weight loss and central nervous system depression and debilitation occurred in 16% of the rats receiving 300 mg/kg/day for 3 to 4 days (Dow Chemical Company 1988). Rats orally administered a single dose of 100 mg/kg displayed necrosis and fatty degeneration of the liver, increased serum leucine aminopeptidase, increased liver ascorbic acid, and increased liver triglyceride levels (Schmidt et al. 1980a). Rats orally treated for 17 weeks with a dose of 3.2;mg/kg/day exhibited chronic inflammation of the kidney (Gohlke et al. 1977). Rats had a body weight loss of 38% for the males and 24% for the females after 6 weeks of 178 mg/kg/day but apparently recovered by the end of the 78-week treatment regiment (NCI 1978). At the 280 mg/kg/day dosage, rats died after 70 weeks. At the end of the 78 weeks of 284 mg/kg/day, male mice died of tubular nephrosis and female mice demonstrated hydronephrosis (NCI 1978). [These NCI (1978)dosages were time-weighted averages of the different doses given.] An oral reference dose (RfD) is under review by the United States Environmental Protection Agency (EPA 1995a).

Lethal exposure concentrations and exposure times for rats were approximately 1000 ppm after 4 to 6 hours (Carpenter et al. 1949, Deguchi 1972, Schmidt et al. 1980b, Smyth et al. 1969) and 5100;ppm after 30 minutes (Price et al. 1978). One of 10 rats exposed to 6300 ppm for 30 minutes exhibited myocardial damage (Price et al. 1978). Mice exposed to 600 ppm for 3 hours developed fatty changes in the liver (Tomokuni 1969, 1970; Hayrack et al. 1962). Exposure of rats to 130 ppm for 15 weeks

resulted in increased liver weights, granulation and vacuolization of the liver, and liver hyperplasia (Truffert et al. 1977). Rabbits exposed to 15 ppm for 7 to 11 months exhibited signs of liver degeneration (Navrotskiy et al. 1971). One monkey exposed to a time-weighted average of 1974;ppm for 2 hours/day, 6 days/week for 9 months (no control) had transient diarrhea, anorexia, centrilobular vacuolization, and fatty degeneration of the liver (Hayrack et al. 1962). An inhalation reference concentration (RfC) has not been derived.

The dermal LD_{50} value in rabbits was determined to be 6.36 g/kg (Smyth et al. 1969). Thickening of the cellular nucleus and pseudoeosinophilic infiltration was observed after dermal application of 514 mg/cm^2 for 16 hours on guinea pigs (Kronevi et al. 1981).

Army workers exposed to 1,1,2,2-tetrachloroethane vapor in a clothing processing plant had a very slight increase in death due to genital cancers, leukemia, or other lymphomas than workers not employed in a clothing plant (Norman et al. 1981). Male and female mice orally administered 142 and 284 mg/kg/day for 78 weeks had an increase in hepatocellular carcinomas (NCI 1978). Based on these results, 1,1,2,2-tetrachloroethane has been classified as Group C, possible human carcinogen (EPA;1995b). For oral exposures, the slope factor is 0.2 $(mg/kg/day)^{-1}$, and the unit risk is 5.8E-06;$(g/L)^{-1}$ (EPA 1995a). For inhalation exposures, the slope factor is 0.2 $(mg/kg/day)^{-1}$ (EPA;1995b), and the unit risk is 5.8E-05 $(g/m^3)^{-1}$ (EPA 1995a).

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Toxicity Profiles

Toxicity Summary for 1,1,1-TRICHLOROETHANE

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

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1,1,1-Trichloroethane is absorbed via the inhalation, oral, and dermal exposure routes (ATSDR 1995). After cessation of exposure, clearance of the chemical from the blood is rapid; 60 to 80% is eliminated within 2 hours, and greater than 95% is eliminated within 50 hours (Monster et al. 1979, Nolan et al. 1984). A large fraction of the absorbed dose is excreted unchanged in exhaled air, regardless of route of exposure (Torkelson 1994).

The distribution of absorbed 1,1,1-trichloroethane is similar for all routes of exposure. The chemical has been detected in the fat, liver, lung, and muscle of humans and in the fat, liver, kidney, brain, muscle, and skin of

animals (Alles et al. 1988, Holmberg et al. 1977, Savolainen et al., 1977, Schumann et al. 1982, Takahara 1986). Humans and animals metabolize less than 10% of a dose of 1,1,1-trichloroethane regardless of the route of exposure; the major urinary metabolites are trichloroethanol and its glucuronide conjugate, trichloroacetic acid, and volatile carbon dioxide (ATSDR 1995, Nolan et al. 1984). These urinary metabolites are excreted slowly in comparison to the rate of expiration of 1,1,1-trichloroethane in the breath (elimination half-times, 10 to 27 and 70 to 85 hours, respectively), and may accumulate with repeated exposure, such as in the workplace (Nolan et al. 1984).

Few data were found for the oral toxicity of 1,1,1-trichloroethane. One case study reported gastrointestinal and hepatic effects in an individual who accidentally ingested approximately 600 mg/kg of the chemical (Stewart and Andrews 1966). In animals, oral LD_{50} values range from 5660 mg/kg (rabbits) to 12,300 mg/kg (rats) (Torkelson et al. 1958). Death in most cases has been attributed to central nervous system depression resulting from anesthesia. Chronic oral doses of $1500 mg/kg reduced body weight gain and increased the effects of aging in rats and reduced body weight gain and decreased survival in mice (NCI 1977). No other effects were noted in either species.

In both humans and animals, the first and primary response to acute, high concentrations of inhaled 1,1,1-trichloroethane is central nervous system depression. The chemical also can sensitize the heart to epinephrine at high levels but has little effect on other organs. Accidental exposures to concentrations ranging from 6000 to 20,000 ppm have been fatal to humans (ATSDR 1995, Torkelson 1994).

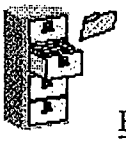
The effects of subchronic and chronic inhalation exposure to 1,1,1-trichloroethane are generally mild, characterized by growth reduction in guinea pigs (650 ppm) (Adams et al. 1950) and minimal hepatic effects in mice (247 ppm, continuous exposure) and rats (1500 ppm, intermittent exposure) (McNutt et al. 1975, Quast et al. 1988). At 1000 ppm for 7 hours/day, 5 days/week for 6 months, female guinea pigs had fatty liver changes and increased liver weights; the no observed adverse effects level was 500 ppm (Torkelson et al. 1958). Fatty liver in humans has been associated with exposure to 1,1,1-trichloroethane (Hodgson et al. 1989).

One epidemiology study and several animal studies did not establish a relationship between exposure to 1,1,1-trichloroethane and adverse developmental or reproductive effects (Wrensch et al. 1990, Riddle et al. 1981, Verschuuren and de Rooij 1990).

The subchronic and chronic oral RfD values for 1,1,1-trichloroethane were withdrawn from the Integrated Risk Information System database on August 1, 1991 (EPA 1995a) and from *Health Effects Assessment Summary Tables* (EPA 1995b). A provisional chronic inhalation reference

concentration value of 1 mg/m^3 has been recommended (EPA 1995c) based on fatty liver changes in guinea pigs.

Regarding the carcinogenicity of 1,1,1-trichloroethane, oral bioassays were inconclusive and inhalation studies were negative (NCI 1977, Maltoni et al. 1986, Rampy et al. 1977, Quast et al. 1988). No epidemiological data for 1,1,1-trichloroethane and inadequate carcinogenicity data for animals place the chemical in the United States Environmental Protection Agency's weight-of-evidence group D, not classifiable as to human carcinogenicity (EPA 1995a).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Toxicity Summary for TRICHLOROETHENE

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

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Prepared for: Oak Ridge Reservation Environmental Restoration Program.

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Trichloroethene (TCE) is an industrial solvent used primarily in metal degreasing and cleaning operations. TCE can be absorbed through the lungs, mucous membranes, gastrointestinal tract, and the skin. TCE is extensively metabolized in humans to trichloroacetic acid and trichloroethanol, as well as to several minor metabolites, with most of the absorbed dose excreted in urine (ATSDR, 1989; U.S. EPA, 1985).

Human and animal data indicate that exposure to TCE can result in toxic effects on a number of organs and systems, including the liver, kidney, blood, skin, immune system, reproductive system, nervous system, and cardiovascular system. In humans, acute inhalation exposure to TCE causes central nervous system symptoms such as headache, dizziness, nausea, and unconsciousness (U.S. EPA, 1985). Among the reported effects from occupational exposure studies are fatigue, light-headedness,

sleepiness, vision distortion, abnormal reflexes, tremors, ataxia, nystagmus, increased respiration, as well as neurobehavioral or psychological changes. Cardiovascular effects include tachycardia, extrasystoles, EKG abnormalities, and precordial pain (Landrigan et al., 1987; Grandjean et al., 1955; Milby, 1968). The use of TCE as an anesthetic has been associated with cardiac arrhythmias (U.S. EPA, 1985).

Cases of severe liver and kidney damage, including necrosis, have been reported in humans following acute exposure to TCE (Defalque, 1961), but these effects generally are not associated with long-term occupational exposures. In animals, TCE has produced liver enlargement with hepatic biochemical and/or histological changes (Nomiyama et al., 1986; Kjellstrand et al., 1981, 1983; Stott et al., 1982; Tucker et al., 1982) and kidney enlargement, renal tubular alterations and/or toxic nephropathy (NTP, 1982, 1986a, 1988). Also observed in animals were hematological effects (Tucker et al., 1982; Mazza and Brancaccio, 1967) and immunosuppression (Sanders et al., 1982). Inhalation studies with rats indicate that TCE is a developmental toxicant causing skeletal ossification anomalies and other effects consistent with delayed maturation (Healy et al., 1982; Dorfmueller et al., 1979). TCE may cause dermatitis and dermographism (U.S. EPA, 1985).

Reference Doses (RfDs) and Reference Concentrations (RfCs) for subchronic and chronic oral and inhalation exposure to TCE are presently under review by EPA (U.S. EPA, 1992a).

Epidemiologic studies have been inadequate to determine if a correlation exists between exposure to TCE and increased cancer risk. Chronic oral exposure to TCE increased the incidences of hepatocellular carcinomas in mice and renal adenocarcinomas and leukemia in rats (NTP, 1988; Maltoni et al., 1986; NTP, 1986a, 1982; NCI, 1976). Chronic inhalation exposure induced lung and liver tumors in mice and testicular Leydig cell tumors in rats (Maltoni et al., 1986, 1988; Fukuda et al., 1983; Bell et al., 1978). Although U.S. EPA's Science Advisory Board recommended a weight-of-evidence classification of C-B2 continuum (C = possible human carcinogen; B2 = probable human carcinogen), the agency has not adopted a current position on the weight-of-evidence classification (U.S. EPA, 1992b). In an earlier evaluation, TCE was assigned to weight-of-evidence Group B2, probable human carcinogen, based on tumorigenic responses in rats and mice for both oral and inhalation exposure and on inadequate data in humans (U.S. EPA, 1987, 1990). Carcinogen slope factors are 1.1E-2 $(mg/kg/day)^{-1}$ and 6.0E-3 $(mg/kg/day)^{-1}$ for oral and inhalation exposure, respectively. The corresponding unit risks are 3.2E-7 $(\mu g/L)^{-1}$ and 1.7E-6 $(\mu g/m^3)^{-1}$, respectively (U.S. EPA, 1992b).

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Toxicity Summary for ZINC AND ZINC COMPOUNDS

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

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Zinc is used primarily in galvanized metals and metal alloys, but zinc compounds also have wide commercial applications as chemical intermediates, catalysts, pigments, vulcanization activators and accelerators in the rubber industry, UV stabilizers, and supplements in animal feeds and fertilizers. They are also used in rayon manufacture, smoke bombs, soldering fluxes, mordants for printing and dyeing, wood preservatives, mildew inhibitors, deodorants, antiseptics, and astringents (Lloyd, 1984; ATSDR, 1989). In addition, zinc phosphide is used as a rodenticide.

Zinc is an essential element with recommended daily allowances ranging from 5 mg for infants to 15 mg for adult males (NRC, 1989).

Gastrointestinal absorption of zinc is variable (20-80%) and depends on the chemical compound as well as on zinc levels in the body and dietary concentrations of other nutrients (U.S. EPA, 1984). In individuals with normal zinc levels in the body, gastrointestinal absorption is 20-30% (ATSDR, 1989). Information on pulmonary absorption is limited and complicated by the potential for gastrointestinal absorption due to

mucociliary clearance from the respiratory tract and subsequent swallowing. Zinc is present in all tissues with the highest concentrations in the prostate, kidney, liver, heart, and pancreas. Zinc is a vital component of many metalloenzymes such as carbonic anhydrase, which regulates CO_2 exchange (Stokinger, 1981). Homeostatic mechanisms involving metallothionein in the mucosal cells of the gastrointestinal tract regulate zinc absorption and excretion (ATSDR, 1989).

In humans, acutely toxic oral doses of zinc cause nausea, vomiting, diarrhea, and abdominal cramps and in some cases gastric bleeding (Elinder, 1986; Moore, 1978; ATSDR, 1989). Ingestion of zinc chloride can cause burning in the mouth and throat, vomiting, pharyngitis, esophagitis, hypocalcemia, and elevated amylase activity indicative of pancreatitis (Chobanian, 1981). Zinc phosphide, which releases phosphine gas under acidic conditions in the stomach, can cause vomiting, anorexia, abdominal pain, lethargy, hypotension, cardiac arrhythmias, circulatory collapse, pulmonary edema, seizures, renal damage, leukopenia, and coma and death in days to weeks (Mack, 1989). The estimated fatal dose is 40 mg/kg. Animals dosed orally with zinc compounds develop pancreatitis, gastrointestinal and hepatic lesions, and diffuse nephrosis.

Gastrointestinal upset has also been reported in individuals taking daily dietary zinc supplements for up to 6 weeks (Samman and Roberts, 1987). There is also limited evidence that the human immune system may be impaired by subchronic exposures (Chandra, 1984). In animals, gastrointestinal and hepatic lesions, (Allen et al., 1983; Brink et al., 1959); pancreatic lesions (Maita et al., 1981; Drinker et al., 1927a); anemia (ATSDR, 1989; Fox and Jacobs, 1986; Maita et al., 1981); and diffuse nephrosis (Maita et al., 1981; Allen et al., 1983) have been observed following subchronic oral exposures.

Chronic oral exposures to zinc have resulted in hypochromic microcytic anemia associated with hypoceruloplasminemia, hypocupremia, and neutropenia in some individuals (Prasad et al., 1978; Porter et al., 1977). Anemia and pancreatitis were the major adverse effects observed in chronic animal studies (Aughey et al., 1977; Drinker et al., 1927a; Walters and Roe, 1965; Sutton and Nelson, 1937). Teratogenic effects have not been seen in animals exposed to zinc; however, high oral doses can affect reproduction and fetal growth (Ketcheson et al., 1969; Schlicker and Cox 1967, 1968; Sutton and Nelson, 1937).

The reference dose for chronic oral exposure to zinc is under review by EPA; the currently accepted RfD for both subchronic and chronic exposures is 0.2 mg/kg/day based on clinical data demonstrating zinc-induced copper deficiency and anemia in patients taking zinc sulfate for the treatment of sickle cell anemia (U.S. EPA, 1992). The chronic oral RfD for zinc phosphide is 0.0003 mg/kg/day (U.S. EPA, 1991a), and the subchronic RfD is 0.003 mg/kg/day (U.S. EPA, 1992).

Under occupational exposure conditions, inhalation of zinc compounds (mainly zinc oxide fumes) can result in a condition identified as "metal fume fever", which is characterized by nasal passage irritation, cough, rales, headache, altered taste, fever, weakness, hyperpnea, sweating, pains in the legs and chest, leukocytosis, reduced lung volume, and decreased diffusing capacity of carbon monoxide (ATSDR, 1989; Bertholf, 1988). Inhalation of zinc chloride can result in nose and throat irritation, dyspnea, cough, chest pain, headache, fever, nausea and vomiting, and respiratory disorders such as pneumonitis and pulmonary fibrosis (ITII, 1988; ATSDR, 1989; Nemery, 1990). Pulmonary inflammation and changes in lung function have also been observed in inhalation studies on animals (Amur et al., 1982; Lam et al., 1985; Drinker and Drinker, 1928).

Although "metal fume fever" occurs in occupationally exposed workers, it is primarily an acute and reversible effect that is unlikely to occur under chronic exposure conditions when zinc air concentrations are less than 8-12 mg/m^3 (ATSDR, 1989). Gastrointestinal distress, as well as enzyme changes indicative of liver dysfunction, have also been reported in workers occupationally exposed to zinc (NRC, 1979; Stokinger, 1981; U.S. EPA, 1991a; Guja, 1973; Badawy et al., 1987a); however, it is unclear as to what extent these effects might have been caused by pulmonary clearance, and subsequent gastrointestinal absorption. Consequently, there are no clearly defined toxic effects that can be identified as resulting specifically from pulmonary absorption following chronic low level inhalation exposures. Animal data for chronic inhalation exposures are not available.

An inhalation reference concentration has not been derived for zinc or zinc compounds (U.S. EPA, 1992).

No case studies or epidemiologic evidence has been presented to suggest that zinc is carcinogenic in humans by the oral or inhalation route (U.S. EPA, 1991a). In animal studies, zinc sulfate in drinking water or zinc oleate in the diet of mice for a period of one year did not result in a statistically significant increase in hepatomas, malignant lymphomas, or lung adenomas (Walters and Roe, 1965); however, in a 3-year, 5-generation study on tumor-resistant and tumor-susceptible strains of mice, exposure to zinc in drinking water resulted in increased frequencies of tumors from the F_0 to the F_4 generation in the tumor-resistant strain (from 0.8 to 25.7%, vs. 0.0004% in the controls), and higher tumor frequencies in two tumor-susceptible strains (43.4% and 32.4% vs. 15% in the controls) (Halme, 1961).

Zinc is placed in weight-of-evidence Group D, not classifiable as to human carcinogenicity due to inadequate evidence in humans and animals (U.S. EPA, 1991a).

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Toxicity Profiles

Toxicity Summary for XYLENE

NOTE: Although the toxicity values presented in these toxicity profiles were correct at the time they were produced, these values are subject to change. Users should always refer to the Toxicity Value Database for the currect toxicity values.

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Prepared for OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM

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Xylene (dimethylbenzene) is a colorless, flammable liquid that is used as a solvent in the printing, rubber, and leather industries and as a cleaner and paint thinner. It occurs naturally in petroleum and coal tar. Xylene is absorbed following oral, dermal, or inhalation exposure; can be stored in adipose tissue; and is eliminated in the urine after conjugation with glycine.

Human exposure to xylene by either oral or inhalation routes can cause death due to respiratory failure accompanied by pulmonary congestion (Sandmeyer, 1981). Nonlethal levels of xylene vapor may cause eye (Carpenter et al., 1975), nose, and throat (ATSDR, 1993) irritation, and contact with liquid may result in dermatitis (Sittig, 1985). Chronic occupational exposure to xylene has been associated with headaches, chest pain, electrocardiographic abnormalities, dyspnea, cyanosis of

hands, fever, leukopenia, malaise, impaired lung function, and confusion (Hipolito, 1980).

Long-term gavage studies with mixed xylenes in laboratory animals resulted in decreased body weight gain in male rats given 500 mg/kg/day and hyperactivity in male and female mice given 1000 mg/kg/day (NTP, 1986). A chronic oral reference dose (RfD) of 2 mg/kg/day for mixed xylenes was calculated from a no-observed-adverse-effect level (NOAEL) of 250 mg/kg/day derived from a chronic gavage study with rats (EPA, 1994a). The critical effects were hyperactivity, decreased body weight, and increased mortality (males). An RfD of 2 mg/kg/day is also reported for the *m*- and *o*-xylene isomers (EPA, 1994b).

Inhalation of 3000 mg/m^3 of the *o*-, *p*-, or *m*-xylene isomer by rats on gestation days 7-14 resulted in decreased fetal weights, skeletal anomalies, and altered fetal enzyme activities (Hood and Ottley, 1988). Rib anomalies and cleft palate occurred in mouse fetuses following maternal oral exposure of 2.06 g/kg/day of mixed xylenes on gestation days 6-15 (Marks et al., 1982). An inhalation reference concentration (RfC) is under review by EPA (1994a).

Oral (NTP, 1986) and topical (Berenblum, 1941; Pound, 1970) carcinogenic studies with xylene in laboratory animals gave negative results. EPA (1994a) has placed xylene in weight-of-evidence group D, not classifiable as to human carcinogenicity. No significant increase in tumor incidence was observed in rats or mice of both sexes following oral administration of technical grade xylene.


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