

²¹ U.S. EPA. Office of Drinking Water. 1988. Atrazine health advisory. Washington, D.C.

Bis(2-Chloroethyl)ether

Bis(2-chloroethyl)ether is a colorless nonflammable liquid with a strong unpleasant odor (ATSDR, 1997). The odor threshold for bis(2-chloroethyl)ether is 0.049 ppm (Amoore and Hautala, 1983). The chemical formula for bis(2-chloroethyl)ether is $C_4H_8Cl_2O$, and it has a molecular weight of 143.04 g/mol (ATSDR, 1997). The vapor pressure for bis(2-chloroethyl)ether is 0.71 mm Hg at 20 EC, and it has a log octanol/water partition coefficient ($\log K_{ow}$) of 1.58. Bis(2-chloroethyl)ether is primarily used as a chemical intermediate for the manufacture of pesticides. A small amount of bis(2-chloroethyl)ether is used as a solvent. In the past, bis(2-chloroethyl)ether was used as a solvent for fats, waxes, greases, and esters. It has also been used as a constituent of paints and varnishes, as a cleaning fluid for textiles, and in the purification of oils and gasoline (ATSDR, 1997).

Acute (short-term) inhalation exposure to bis(2-chloroethyl)ether in humans results in extreme irritation of the respiratory tract and skin (ATSDR, 1997; Calabrese and Kenyon, 1991; HSDB, 1993). Animal studies have reported respiratory effects such as irritation of the nose and eyes; congestion, edema, and hemorrhage of the lung; congestion of the brain, liver, and kidneys; and central nervous system (CNS) effects from inhalation exposure to bis(2-chloroethyl)ether (ATSDR, 1997). Acute animal tests, such as the LC_{50} and LD_{50} tests in rats and mice, have shown bis(2-chloroethyl)ether to have high acute toxicity from inhalation and oral exposure and extreme acute toxicity from dermal exposure (ATSDR, 1997; RTECS, 1993).

No information is available on the chronic (long-term) effects of bis(2-chloro-ethyl)ether in humans (ATSDR, 1997). Animal studies have reported decreased body weights in rats exposed to bis(2-chloroethyl)ether orally (ATSDR, 1997). EPA has determined that there are inadequate data for the establishment of an RfC for bis(2-chloroethyl)ether. EPA has not established an RfD for bis(2-chloroethyl)ether.

No information is available on the developmental or reproductive effects of bis(2-chloroethyl)ether in humans (ATSDR, 1997). In one animal study, no effects were observed on the reproductive tissues of the animals, but no tests on reproductive function were performed (ATSDR, 1997).

No information is available on the carcinogenic effects of bis(2-chloroethyl)ether in humans (ATSDR, 1997). Animal studies have reported an increased incidence of liver tumors in mice exposed to bis(2-chloroethyl)ether via oral exposure (Calabrese and Kenyon; USEPA, 1993). EPA has classified bis(2-chloroethyl)ether as a Group B2, probable human carcinogen. EPA uses mathematical models, based on animal studies, to estimate the probability of a person developing cancer from breathing air containing a specified concentration of a chemical. EPA calculated an inhalation unit risk estimate of 3.3×10^{-4} (Fg/m^3)⁻¹. EPA estimates that, if an individual were to breathe air containing bis(2chloroethyl)ether at 0.003 Fg/m^3 * over his or her entire lifetime, that person would theoretically have no more than a one-in-a-million increased chance of developing cancer as a direct result of breathing air containing this chemical. Similarly, EPA estimates that breathing air containing 0.03 Fg/m^3)

Agency for Toxic Substances and Disease Registry (ATSDR). *Toxicological Profile for Bis(2-Chloroethyl)ether* (Draft). U.S. Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 1997.

E.J. Calabrese and E.M. Kenyon. *Air Toxics and Risk Assessment*. Lewis Publishers, Chelsea, MI. 1991.

U.S. Department of Health and Human Services. Hazardous Substances Data Bank (HSDB, online database). National Toxicology Information Program, National Library of Medicine, Bethesda, MD. 1993.

U.S. Department of Health and Human Services. Registry of Toxic Effects of Chemical Substances (RTECS, online database). National Toxicology Information Program, National Library of Medicine, Bethesda, MD. 1993.

U.S. Environmental Protection Agency. *Health Effects Assessment for Bis(2-Chloroethyl)ether*. EPA/600/8-88/023. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Cincinnati, OH. 1993.

J.E. Amore and E. Hautala. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *Journal of Applied Toxicology*, 3(6):272-290. 1983.

bis(2-Ethylhexyl)phthalate

Bis(2-ethylhexyl)phthalate, often referred to as Di(2-ethylhexyl)phthalate (DEHP), exists as a colorless, oily liquid at room temperature. It is used industrially as a plasticizer for resins, to make plastic materials more flexible. DEHP is contained in many plastic products such as imitation leather, rainwear, footwear and toys. It is used in the manufacture of tubing and containers used for blood transfusions and kidney dialysis. DEHP is also used in the manufacture of organic pump fluids in electrical capacitors. DEHP may migrate into the environment under improper use/disposal conditions. As a result, exposure could occur via air, water and food. Patients receiving blood transfusions or kidney dialysis can also be exposed to DEHP (ATSDR, 1997; Sittig, 1981).

DEHP is readily absorbed through ingestion and inhalation and poorly absorbed through the skin. DEHP is largely metabolized prior to intestinal absorption, via hydrolysis, to its corresponding monoester metabolite (MEHP), with the release of 2-ethylhexanol. Once absorbed, DEHP and its metabolites are distributed throughout the body, with most of the compounds initially going to the liver. In general, DEHP and its metabolites are converted to more polar derivatives and are then excreted. DEHP is rapidly cleared from the body, with little potential for accumulation. There are differences in the way DEHP is metabolized among species. Although phase I reactions are essentially the same across species except for quantitative differences, phase II reactions differ among species as to the ability to glucuronidate DEHP and its metabolites. The relationship between pharmacokinetics and toxicity is not known due to gaps in knowledge regarding mechanisms of toxic action (ATSDR, 1997).

Acute toxicity from DEHP is relatively low by both inhalation and ingestion. A 1-hr exposure to 23,670 mg/m³ DEHP did not result in any deaths. The oral LD50 for DEHP ranges from 26,000 to 49,000 mg/kg (ATSDR, 1997). Exposure to DEHP has produced irritation of the eyes, and mucous membranes, nausea and diarrhea (Sittig, 1981). Liver biopsies from dialysis patients showed liver abnormalities (peroxisome proliferation) (ATSDR, 1997). Most of the toxicity data for DEHP originate from animal studies.

Laboratory studies indicate that DEHP targets the liver and the testes. DEHP, administered at high levels, has induced morphological and biochemical liver changes in a number of rodent studies. Both DEHP and MEHP, its metabolite, have also been shown to produce reduced organ weight and damage to the seminiferous tubules of the testes. DEHP has also produced developmental and reproductive effects in laboratory rodents. Developmental effects include exencephaly and spina bifida. Reproductive effects include reduced fertility and fewer and smaller litters (ATSDR, 1997).

There is a large database on the mutagenicity of DEHP involving a large number of tests conducted in bacterial systems as well as in vivo and in vitro mammalian test systems. In addition, a less extensive database is available on the mutagenicity of the metabolites, MEHP and 2-ethylhexanol. The overall weight of evidence indicates that DEHP is not mutagenic (ATSDR, 1997). A carcinogenic feeding bioassay conducted by the National Toxicology Program (NTP) in B6C3F1 mice and F344 rats found an increased incidence of hepatocellular tumors which increased with increasing dose (NTP, 1982). EPA has designated DEHP as a B2, Probable Human Carcinogen.

Agency for Toxic Substances and Disease Registry (ATSDR) (1997) Toxicological profile for di(2-ethylhexyl)phthalate. U.S. Public Health Service.

NTP (1982) Carcinogenesis bioassay of DEHP (CAS No. 117-81-7) in F344 rats and B6C3F1 mice (feed study). National Toxicology Program, Research Triangle Park, NC. NTP-80-37. NIH Publication 82-1772.

Sittig, M. (1981) Handbook of Toxic and Hazardous Chemicals. Noyes Publications.

Naphthalene and 2-Methylnaphthalene

Naphthalene and 2-methylnaphthalene are members of the polycyclic aromatic hydrocarbon family. They are ubiquitous in nature and are both naturally occurring and man-made. Because the database for toxicological information on 2-methylnaphthalene is limited, its toxicity is generally assumed to be approximated by that of naphthalene.

Naphthalene is a white solid substance at room temperature. It has a distinct odor of mothballs or tar. Humidity and sunshine cause evaporation into the air within a few hours. When placed in water or soil, bacteria will destroy naphthalene, or will render it airborne within a few hours (ATSDR, 1997). Tobacco smoke is known to release 3 ug of naphthalene per cigarette (U.S. EPA, 1982). The compound is used in the production of dyes, solvents, lubricants, motor fuels (U.S. EPA, 1980) and is a major component of many moth ball preparations.

Humans can absorb naphthalene by dermal, inhalation and oral routes. Metabolism occurs via the P450 mixed function oxidase enzyme system to yield multiple intermediates which are then conjugated. Key metabolites are responsible for each toxicity endpoint following intraperitoneal administration: 2-naphthoquinones --> hemolysis; 1,2-naphthoquinones --> cataracts; 3-GSH adducts --> pulmonary toxicity (Buckpitt et al., 1984). Excretion of metabolites occurs via urine and feces (ATSDR, 1997).

Adults and children exposed to airborne naphthalene experience vomiting, abdominal pain and anemia (ATSDR, 1997). Most of the data is for inhalation of naphthalene from mothballs. The primary site of toxicity is the erythrocyte resulting in hemolytic crisis (hemolytic anemia). Jaundice is seen upon dermal, inhalation, and oral exposures, as are kidney effects (ATSDR, 1997). Near-blindness resulted in male and female subjects with 5 gram ingestion (ATSDR, 1997).

Oral doses in rats have hepatic effects. Dogs (1800 mg/kg) for 5 days of exposure showed signs of lethargy and ataxia, and decreased hemoglobin levels (ATSDR, 1997).

No studies of genotoxic effects in humans or laboratory animals were located. No human epidemiological evidence for cancer. Inconclusive evidence for cancer in rats and mice were found (ATSDR, 1997).

Agency for Toxic Substances and Disease Registry (ATSDR) (1997) Toxicological profile for naphthalene and 2-methylnaphthalene. U.S. Public Health Service.

Buckpitt, A. and Richieri, P. (1984) Comparative biochemistry and metabolism: Part 2. Naphthalene lung toxicity. Wright-Patterson Air Force Base, OH: Air Force Systems Command, Aerospace Medical Division. Air Force Aerospace Medical Research Laboratory. AFAMRL-TR-84-058.

U.S. Environmental Protection Agency (U.S. EPA) (1980) Ambient water quality criteria for polycyclic aromatic hydrocarbons. Office of Emergency and Remedial Response. Washington, DC.

Nitrobenzene

Nitrobenzene is a pale yellow liquid with an odor of bitter almonds (Dunlap, 1981). Most of the nitrobenzene produced is used as an intermediate in the synthesis of aniline. An anthropogenic environmental contaminant, nitrobenzene can be released to wastewater and air from industrial sources (ATSDR, 1997). It is primarily removed from the environment by photolysis, reaction with hydroxyl radicals, volatilization, and biodegradation (U.S. EPA, 1985).

Nitrobenzene can be absorbed by humans following oral, inhalation, or dermal exposure (U.S. EPA, 1980). When absorbed into the blood, nitrobenzene oxidizes the iron in hemoglobin to form methemoglobin, thus decreasing the oxygen carrying capacity of the blood. The primary systemic effect associated with human exposure to nitrobenzene is methemoglobinemia. Acute oral exposure has resulted in methemoglobinemia, cyanosis, and anemia, and neurological

effects, including headache, nausea, vertigo, confusion, unconsciousness, apnea, coma, and death (Piotrowski, 1967; U.S. EPA, 1980; ATSDR, 1997). Methemoglobinemia has also been reported following subchronic to chronic occupational exposure to nitrobenzene. Additional effects included sulfhemoglobinemia, presence of Heinz bodies in erythrocytes, liver toxicity (hepatomegaly, jaundice, and altered serum chemistry), spleen enlargement, and neurological symptoms (headache, nausea, weakness, vertigo, numbness of legs, and hyperalgesia of hands and feet) (U.S. EPA, 1980; Ikeda and Kita, 1964). Dermal exposure to nitrobenzene has resulted in contact dermatitis (Beauchamp et al., 1982).

Effects observed in subchronic inhalation studies with rodents exposed to nitrobenzene at concentrations up to 50 ppm for 90 days included methemoglobinemia, splenic lesions (splenomegaly, increased hemosiderosis and hematopoiesis), liver toxicity (hepatocyte hyperplasia and focal necrosis), kidney nephrosis, and testicular degeneration. Morphologic changes of the adrenal cortex were reported for mice (CIIT, 1984). Effects on the spleen, kidneys, and liver were also reported in rodents exposed to concentrations up to 125 ppm for 14 days. In addition, there was morphologic damage to the hind brain (Medinsky and Irons, 1985). Testicular degeneration and decreased sperm levels were reported in a two-generation reproductive study with rats (Dodd et al., 1987).

A reference dose (RfD) of $5E-3$ mg/kg/day for subchronic oral exposure and $5E-4$ mg/kg/day for chronic oral exposure to nitrobenzene was calculated from a lowest-observed-adverse-effect level (LOAEL) of 25 mg/m³ derived from a 90-day inhalation study with F344 rats and B6C3F₁ mice (CIIT, 1984). The critical effects were hematological changes in F344 rats, and adrenal, renal, and hepatic lesions in B6C3F₁ mice. Because this value is based on a route to route extrapolation, the RfD may change pending further review by EPA. The same study (CIIT, 1984) served as the basis of a reference concentration (RfC) of $2E-2$ mg/m³ for subchronic inhalation exposure and $2E-03$ mg/m³ for chronic inhalation exposure to nitrobenzene. This value is currently under review by an EPA work group.

No suitable cancer bioassays or epidemiological studies are available to assess the carcinogenicity of nitrobenzene. Therefore, U.S. EPA has placed nitrobenzene in weight-of-evidence group D, not classifiable as to human carcinogenicity.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Nitrobenzene. Prepared by Life Systems, Inc., under Subcontract to Clement Associates, Inc., for ATSDR, U.S. Public Health Service under Contract 205-88-0608. ATSDR/TP-90-19.

Beauchamp, R.O., Jr., R.D. Irons, D.E. Rickert, D.B. Couch and T.E. Hamm, Jr. 1982. A critical review of the literature on nitrobenzene toxicity. *CRC Crit. Rev. Toxicol.* 11: 33-84.

CIIT (Chemical Industry Institute of Toxicology). 1984. Ninety-day inhalation toxicity study of nitrobenzene in F-344 Rats, CD Rats, and B6C3F₁ Mice. Chemical Industry Institute of Toxicology, Research Triangle Park, NC.

Dodd, D.E., E.H. Fowler, W.M. Snellings, et al. 1987. Reproduction and fertility evaluations in CD rats following nitrobenzene inhalation. *Fundam. Appl. Toxicol.* 8: 493-505.

Dunlap, K.L. 1981. Nitrobenzene and nitrotoluenes. In: M. Grayson and D. Eckroth, Eds., Kirk-Othmer Encyclopedia of Chemical Technology, 3rd. ed., Vol. 15. John Wiley and Sons, New York, NY, pp. 916-925.

Ikeda, M. and A. Kita. 1964. Excretion of *p*-nitrophenol and *p*-aminophenol in the urine of a patient exposed to nitrobenzene. Br. J. Ind. Med. 21: 210-213.

Medinsky, M.A. and R.D. Irons. 1985. Sex, strain, and species differences in the response to nitrobenzene vapors. In: Rickert, D.E., Ed., Chemical Industry Institute of Toxicology Series. Toxicity of nitroaromatic compounds. Hemisphere Publishing Corporation, New York, NY, pp. 35-51. Morgan, K.T., E.A. Gross, O. Lyght, et al. 1985. Morphologic and biochemical studies of a nitrobenzene-induced encephalopathy in rats. Neurotoxicology 6: 105-116.

Piotrowski, J. 1967. Further investigations on the evaluation of exposure to nitrobenzene. Br. J. Ind. Med. 24: 60-67.

Piotrowski, J. 1977. Exposure tests for organic compounds in industrial toxicology. NIOSH 77-144. U.S. Department of Health and Human Services.

U.S. EPA. 1980. Ambient Water Quality Criteria for Nitrobenzene. Office of Water Regulations and Standards, Criteria and Standards Division Washington, DC. EPA 440/5-80-061. NTIS PB81-117723.

U.S. EPA. 1985. Health and Environmental Effects Profile for Nitrobenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. ECAO-CIN-P145.

Pentachlorophenol

Pentachlorophenol, a man-made organic biocide, is often contaminated with other toxic organic chemicals such as chlorinated phenols, dioxins, and dibenzofurans (Williams, 1982; U.S. Air Force, 1989; ATSDR, 1997).

Pentachlorophenol is readily absorbed following oral or inhalation exposure and is widely and rapidly distributed throughout the body (Wagner et al., 1991; ATSDR, 1997; Jorens and Schepens, 1993). Human and animal studies have provided evidence indicating that pentachlorophenol is metabolized to various conjugated metabolites. Both the parent compound and the conjugates are excreted in the urine (Braun et al., 1979).

Assessing the potential toxicity of technical (commercial) grade pentachlorophenol is complicated by the presence of the toxic impurities that are usually present, and the effects resulting from occupational exposure are often difficult to attribute to a specific route of exposure (Jorens and Schepens, 1993). The effects in humans following acute oral exposure include increased heart and respiratory rates, elevated temperature, increased basal metabolic rate, and death (29 and 401 mg/kg) (RTECS, 1989).

Human fatalities and toxic effects including tachycardia, jaundice, and other hematologic alterations have been reported for acute and subchronic occupational (e.g., sawmill workers, herbicide sprayers) inhalation exposures to pentachlorophenol. Upper respiratory tract inflammation and bronchitis were reported for sawmill workers chronically exposed to pentachlorophenol (Baader and Bauer, 1951; Menon et al., 1958; ATSDR, 1997). However, dose-terms for these exposures were not available, and concurrent exposures to other chemicals make definitive assessments impossible.

Data regarding the dermal exposure of humans to pentachlorophenol are anecdotal or equivocal, lack dose terms, and are compromised by concurrent exposures to other chemicals including the known contaminants in technical-grade pentachlorophenol. Acute exposure to 0.4% pentachlorophenol produced localized irritation (Bevenue et al., 1967), and subchronic exposures have caused chloracne (Baader and Bauer, 1951; O'Malley et al., 1990) and possibly renal damage (ATSDR, 1997). Dermal lesions including pemphigus and chronic urticaria have been reported for humans chronically exposed to pentachlorophenol-treated wood (Lambert et al., 1986). There currently are no definitive data regarding reproductive toxicity in humans exposed to pentachlorophenol.

Acute oral exposure of animals to pentachlorophenol affects the liver, kidneys, cardiovascular system, and the peripheral and central nervous system. Oral LD₅₀ values for laboratory animals range from 27 to 230 mg/kg (Borzelleca et al., 1985; U.S. Air Force, 1989; ATSDR, 1997). Definitive data regarding the effects of subchronic or chronic oral exposure of humans to pentachlorophenol are not available. However, subchronic exposure (1 to 8 months) of rats to pentachlorophenol at doses ranging from 5 to 40 mg/kg/day has produced cardiovascular, hematotoxic, renal, hepatic, and immunologic responses (Schwetz et al., 1974, 1978; U.S. Air Force, 1989; ATSDR, 1997). Evidence of reproductive/developmental toxicity (increased resorptions, embryoletality, embryotoxicity, and teratogenicity) have also been observed in rats given pentachlorophenol during gestation (Larsen et al., 1974, 1976; Schwetz et al., 1978).

Because the most significant acute toxic effect of pentachlorophenol is elevated metabolism, a specific target organ or tissue is difficult to identify. However, for subchronic and chronic exposures, toxicity data indicate that the liver, kidney, and cardiovascular system are targets for some of the toxic effects of pentachlorophenol.

Both the chronic and subchronic RfDs for pentachlorophenol are 3.00E-02 mg/kg/day based on a NOAEL of 3 mg/kg/day and a LOAEL of 10 mg/kg/day for histopathologic findings in the liver and kidneys of rats given pentachlorophenol in the diet for 2 years (Schwetz et al., 1978).

Based upon increased incidences of hepatocellular adenomas and carcinomas, adrenal medulla pheochromocytomas, malignant pheochromocytomas, and hemangiosarcomas/hemangiomas in mice, pentachlorophenol is classified by the EPA as a probable human carcinogen (Weight of Evidence Category B2) and has an oral slope factor of 1.2E-01 (mg/kg/day)⁻¹ and an oral unit risk of 3.0E-06 (µg/L)⁻¹. The potential carcinogenicity of pentachlorophenol following inhalation exposure has not been evaluated.

- ATSDR (Agency for Toxic Substances and Disease Registry). 1997. *Toxicologic Profile for Pentachlorophenol*. Update Draft. U.S. Dept. of Health and Human Services, Public Health Service.
- Baader, E. W. and H. J. Bauer. 1951. Industrial intoxication due to pentachlorophenol. *Ind. Med. Surg.* 20: 286-290.
- Bevenue, A., J. Wilson, L.J. Casarett, et al. 1967. A survey of pentachlorophenol content in human urine. *Bull. Environ. Contam. Toxicol.* 2: 319-332.
- Borzelleca, J.F., J. R. Hayes, L. W. Condi, et al. 1985. Acute toxicity of monochlorophenols, dichlorophenols and pentachlorophenols. *Toxicol. Lett* 29: 39-42.
- Braun, W. H., G. E. Blau, and M. B. Chenoweth. 1979. The metabolism/pharmacokinetics of pentachlorophenol in man, and a comparison with the rat and monkey. In: Deichmann, W.E., Ed. *Toxicology and Occupational Medicine*. New York, Amsterdam, Oxford, Elsevier/North-Holland, 289-296.
- Jorens, P. G. and J. C. Schepens. 1993. Human pentachlorophenol poisoning. *Human and Exp. Toxicol.* 12: 479-495.
- Lambert, J., P. Schepens, J. Janssens, et al. 1986. Skin lesions as a sign of subacute pentachlorophenol intoxication. *Acta Derm. Venereol.* (Stockh) 66: 170-172.
- Larsen, R. V. 1976. The placental transfer and teratology of pentachlorophenol in rats. [abstract]. *Diss. Abstr. Int.* B 37: 1184-1185.
- Larsen, R. V., G. S. Born, W. V. Kessler, et al. 1975. Placental transfer and teratology of pentachlorophenol in rats. *Environ. Lett.* 10: 121-128.
- Menon, J. A. 1958. Tropical hazards associated with the use of pentachlorophenol. *Br. Med. J.* 1: 1156-1158.
- NTP (National Toxicology Program). 1989. *Toxicology and carcinogenesis of two pentachlorophenol technical-grade mixtures (CAS No. 87-86-5) in B6C3F₁ mice (feed studies)*, NTP Technical Report No. 349. NIH Publ. No. 89-2804.
- O'Malley, M. A., A. V. Carpenter, M. H. Sweeney, et al. 1990. Chloracne associated with employment in the production of pentachlorophenol. *Am. J. Ind. Med.* 17: 411-421.
- RTECS (Registry for Toxic Effects of Chemical Substances). 1989. *Pentachlorophenol*.
- Schwetz, B.A., Keeler, P.A., Gehring, P.J. 1974. The effect of purified and commercial grade pentachlorophenol on rat embryonal and fetal development. *Toxicol. Appl. Pharmacol.* 28: 151-161.

Schwetz, B. A., J. F. Quast, P. A. Keeler, et al. 1978. Results of two-year toxicity and reproduction studies on pentachlorophenol. In: Rao, K. R., Ed. *Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology*. New York, NY: Plenum Press, 301-309.

U.S. Air Force. 1989. *The Installation Restoration Toxicology Guide. Pentachlorophenol. Vol. 3*, pp. 39-1 - 39-49. Harry G. Armstrong Aerospace Medical Research Laboratory, Air Force Systems Command, Wright-Patterson AFB, OH.

Wagner, S. L., L. R. Durand, R. D. Inman, U. Kiigemagi, and M. L. Deinzer. 1991. Residues of pentachlorophenol and other chlorinated contaminants in human tissues: analysis by electron capture gas chromatography and electron capture negative ion mass spectrophotometry. *Arch. Environ. Contam. Toxicol.* 21: 596-606.

Williams, P.L. 1982. Pentachlorophenol, an assessment of the occupational hazard. *J. Am. Ind. Hyg. Assoc.* 43: 799-810.

Polycyclic Aromatic Hydrocarbons (Carcinogenic)

Polycyclic aromatic hydrocarbons (PAHs) occur in the environment as complex mixtures containing numerous PAHs of varying carcinogenic potencies. Only a few components of these mixtures have been adequately characterized, and only limited information is available on the relative potencies of different compounds.

PAH absorption following oral and inhalation exposure is inferred from the demonstrated toxicity of PAHs following ingestion and inhalation, respectively (USEPA, 1984a). PAHs are also absorbed following dermal exposure (Kao *et al.*, 1985). It has been suggested that simultaneous exposure to carcinogenic PAHs (cPAHs) such as benzo(a)pyrene and particulate matter can increase the effective dose of the compound (ATSDR, 1997). Acute effects from direct contact with PAHs and related materials are limited primarily to phototoxicity; the primary effect is dermatitis (NIOSH, 1977). PAHs have also been shown to cause cytotoxicity in rapidly proliferating cells throughout the body; the hematopoietic system, lymphoid system, and testes are frequent targets (Santodonato *et al.*, 1981). Destruction of the sebaceous glands, hyperkeratosis, hyperplasia, and ulceration have been observed in mouse skin following dermal application of the cPAHs (Santodonato *et al.*, 1981). Benzo(a)pyrene has also been shown to have an immunosuppressive effect in animals (ATSDR, 1997). Nonneoplastic lesions have been observed in animals exposed to the more potent cPAHs, but only after exposure to levels well above those required to elicit a carcinogenic response. Benzo(a)pyrene has been demonstrated to induce adverse developmental and reproductive effects in experimental animals following oral exposure (ATSDR, 1997). These effects were manifested as reduced pup weights during postnatal development, sterility, reduced fertility, and an increased incidence of stillborns and resorptions (ATSDR, 1997). cPAHs are believed to induce tumors both at the site of application and systemically. Studies in laboratory animals have demonstrated that the cPAHs benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, chrysene, dibenz(a,h)anthracene and indeno(1,2,3-cd)pyrene have the ability to induce skin tumors following dermal exposure (ATSDR, 1997). Neal and Rigdon (1967) reported that oral administration of 250 ppm benzo(a)pyrene for approximately 110 days led to forestomach tumors

in mice. Thyssen et al. (1981) observed respiratory tract tumors in hamsters exposed to up to 9.5 mg/m³ benzo(a)pyrene for up to 96 weeks.

Benzo(a)pyrene, benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene, dibenz(a,h)anthracene, and indeno(1,2,3-cd)pyrene are classified by USEPA in Group B2—Probable Human Carcinogen. USEPA has developed an oral slope factor of 7.3 (mg/kg-day)⁻¹ for benzo(a)pyrene based on the geometric mean of four slope factors calculated from three studies (Neal and Rigdon, 1967; Brune *et al.*, 1981; Rabstein *et al.*, 1973). Oral cancer slope factor for the other six cPAHs are derived by applying relative potency factors developed by USEPA (1993) to the oral slope factor for benzo(a)pyrene (benzo(a)anthracene, 0.73 (mg/kg-day)⁻¹; benzo(b)fluoranthene, 0.73 (mg/kg-day)⁻¹; benzo(k)fluoranthene, 0.073 (mg/kg-day)⁻¹; chrysene, 0.0073 (mg/kg-day)⁻¹; dibenz(a,h)anthracene, 7.3 (mg/kg-day)⁻¹; indeno(1,2,3-cd)pyrene, 0.73 (mg/kg-day)⁻¹).

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for polycyclic aromatic hydrocarbons (PAHs)*. U.S. Public Health Service.

Brune, H., R.P. Deutsch-Wenzel, M. Habs, S. Ivankovic and D. Schmhl. 1981. Investigation of the tumorigenic response to benzo(a)pyrene in aqueous caffeine solution applied orally to Sprague-Dawley rats. *J. Cancer Res. Clin. Oncol.* 102:153-57.

Kao, J.K., F.K. Patterson and J. Hall. 1985. Skin penetration and metabolism of topically applied chemicals in six mammalian species including man: An *in vitro* study with benzo[a]pyrene and testosterone. *Toxicol. Appl. Pharmacol.* 81:502-516.

National Institute for Occupational Safety and Health (NIOSH). 1977. *Criteria for a Recommended Standard—Occupational Exposure to Coal Tar Products*. DHEW (NIOSH) 78-107.

Neal, J. and R.H. Rigdon. 1967. Gastric tumors in mice fed benzo(a)pyrene: A quantitative study. *Tex. Rep. Biol. Med.* 25:553-557.

Rabstein, L.S., R.L. Peters and G.H. Spahn. 1973. Spontaneous tumors and pathologic lesions in SWR/J mice. *J. Natl. Cancer Inst.* 50:751-758.

Santodonato, J., P. Howard and D. Basu. 1981. Health and ecological assessment of polynuclear aromatic hydrocarbons. *J. Environ. Pathol. Toxicol.* 5:1-364.

Thyssen, J., J. Althoff, G. Kimmerle and U. Mohr. 1981. Inhalation studies with benzo(a)pyrene in Syrian golden hamsters. *J. Natl. Cancer Inst.* 66:575-577.

U.S. Environmental Protection Agency (USEPA). 1984. *Health effects assessment for polycyclic aromatic hydrocarbons (PAHs)*. Environmental Criteria and Assessment Office. EPA 540/1-86-013. September 1984.

U.S. Environmental Protection Agency (USEPA). 1993. *Provisional guidance for quantitative risk assessment of polycyclic aromatic hydrocarbons*. Office of Research and Development. EPA/600/R-93/089. July 1993.

Phenanthrene

Phenanthrene is a member of the polyaromatic hydrocarbons (PAH). PAHs constitute a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The database on the potential health effects of phenanthrene is limited.

Little data are available regarding the pharmacokinetics of phenanthrene. The intestinal absorption of phenanthrene is less dependent on the presence of bile in the stomach than is the absorption of the larger PAHs (such as benzo(a)pyrene) (Rahman et al, 1986).

Phenanthrene has been shown to be a skin photosensitizer in humans (Sax, 1984). Phenanthrene has a reported LD 50 of 700 mg/kg in mice (Simmon et al., 1979). Rats injected intraperitoneally evidenced liver effects (Yoshikawa et al, 1987).

There is equivocal evidence for cancer from dermal application of phenanthrene in rats (IARC, 1983). Phenanthrene is not a complete skin carcinogen (ATSDR, 1997). It is neither an initiator (LaVoie et al, 1981; Roe, 1962) nor a promoter (Roe and Grant, 1964). Higgins and Yang (1962) reported no tumor production within two months after the ingestion of 200 mg of phenanthrene by rats. There are limited data that suggest that phenanthrene is mutagenic (Wood et al., 1979). However, the majority of tests are negative (ATSDR, 1997).

Agency for Toxic Substances and Disease Registry (ATSDR) (1997) Toxicological profile for polycyclic aromatic hydrocarbons. U. S. Public Health Service.

Higgins, L. and Yang, Y. (1962) *Induction and extinction of mammary cancer*. Science 137:257-262.

International Agency for Research on Cancer (IARC) (1983) *Monograph on the evaluation of carcinogenic risk of chemicals to man, Phenanthrene*. 32:419-430.

LaVoie, K. et al. (1981) *Mutagenicity and tumor initiating activity and metabolism of phenanthrenes*. Cancer Res. 41:3441-3447.

Rahman, A., Barrowman, J.A., Rahimtula, A. (1986) *The influence of bile on the bioavailability of polynuclear aromatic hydrocarbons from the rat intestine*. Can J Physio Pharmacol 64:1214-1218.

Roe, F.J.C. (1962) *Effect of phenanthrene on tumour-initiation by 3,4-benzpyrene*. Br J Cancer 16:503-506.

Sax, N.I. (1984) Dangerous Properties of Industrial Materials. 6th edition. Van Nostrand Reinhold Company. N.Y.

Simmon, P. et al. (1979) *Mutagenic activity of chemicals carcinogens and related compounds in the intraperitoneal host-mediated assay*. J. Natl. Cancer Inst. 62:911-918.

Wood, R. et al. (1979) *Mutagenicity and tumorigenicity of phenanthrene and chrysene epoxides and diol epoxides*. Cancer Res. 39:4069-4077.

Yoshikawa, T. et al. (1987) *Toxicity of polycyclic aromatic hydrocarbons III. Effects of beta-naphthoflavone pretreatment on hepatotoxicity of compounds produced in the ozonation or NO₂-nitration of phenanthrene and pyrene by rats*. Vetern Human Toxicol. 29:113-117.

PESTICIDES AND POLYCHLORINATED BIPHENYLS

Dieldrin

Dieldrin is a chlorinated cyclodiene insecticide that is structurally related to aldrin. Both aldrin and dieldrin are well absorbed through the lungs, skin, and gastrointestinal tract (Shell, 1984; Heath and Vanderkar, 1964; Hunter and Robinson, 1967, 1969; Sundaram *et al.*, 1978a,b; Iatropoulos *et al.*, 1975). Aldrin is metabolically converted to dieldrin in fatty tissues (ACGIH, 1986) and both are considered to have similar chemical and toxic effects (USEPA, 1988). Several human and animal studies have shown that adipose tissue is the primary storage depot for dieldrin, followed by the liver, brain, and whole blood (ATSDR, 1997). Acute symptoms of dieldrin intoxication in humans and animals following ingestion or inhalation indicate CNS stimulation manifested primarily as irritability, salivation, tremors, and convulsions. Experimental studies indicate that dogs exposed for longer periods of time to levels as low as 1 mg/kg developed hepatic and renal toxicity (Fitzhugh *et al.*, 1964; Treon and Cleveland, 1955; Walker *et al.*, 1969). Rats fed dieldrin for 2 years developed hepatic lesions and nephritis at doses of 0.5 and 50 ppm, respectively (Fitzhugh *et al.*, 1964). Dieldrin produced fetotoxic and/or teratogenic effects in hamsters fed a single oral dose of 50 mg/kg (approximately 84 ppm) and in mice fed a single oral dose of 25 mg/kg (approximately 6 ppm) (Ottolenghi *et al.*, 1974). Dieldrin produced marked effects on fertility, gestation, viability, and lactation in mice given 25 mg/kg-day in a six-generation study (Deichmann, 1972). Dieldrin produces chromosomal aberrations in mouse, rat, and human cells and unscheduled DNA synthesis in rats and humans (Probst *et al.*, 1981). Chronic oral exposure to dieldrin has produced an increase in hepatocellular tumors in mice (Davis, 1965; Epstein, 1975; NCI, 1978). In contrast, chronic feeding studies with dieldrin in rats indicate that exposure was associated with nonneoplastic changes in the liver (NCI, 1978; Fitzhugh *et al.*, 1964). Ingestion of dieldrin by laboratory animals results in a decreased immune response (Loose 1982; Loose *et al.*, 1981).

USEPA classified dieldrin as group B2 - Probable Human Carcinogen and developed an oral cancer slope factor of $1.6 \times 10^{+1} \text{ (mg/kg-day)}^{-1}$ based on the increased incidence of liver carcinoma observed in male and female C3H mice (Davis, 1965; Epstein, 1975) and in male B6C3F1 mice (NCI, 1978). USEPA derived a chronic oral RfD for dieldrin of $5 \times 10^{-5} \text{ mg/kg-}$

day based on a study in which rats were fed dieldrin for 2 years and displayed liver lesions at dose levels of 0.005 mg/kg-day (1 ppm) and greater (Walker *et al.*, 1969). An uncertainty factor of 100 was used to calculate the chronic RfD.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological profile for aldrin/dieldrin. U.S. Public Health Service.

American Conference of Governmental Industrial Hygienists (ACGIH). 1986. *Documentation of the threshold limit values and biological exposure indices*. 5th ed. Cincinnati: ACGIH. pp. 17, 196.

Davis, L. 1965. Pathology report on mice fed dieldrin, aldrin, heptachlor, or heptachlor epoxide for two years. Internal FDA memorandum to Dr. A.J. Lehrman, July 19, 1965.

Deichmann, W. 1972. Toxicology of DDT and related chlorinated hydrocarbon pesticides. *J. Occup. Med.* 14:285.

Epstein, S. 1975. The carcinogenicity of dieldrin. Part 1. *Sci. Total Environ.* 4:1-52.

Fitzhugh, O., A. Nelson and M. Quaife. 1964. Chronic oral toxicity of aldrin and dieldrin in rats and dogs. *Food Cosmet. Toxicol.* 2:551-562.

Heath, D. and M. Vandekar. 1964. Toxicity and metabolism of dieldrin in rats. *Br. J. Ind. Med.* 21:269-279.

Hunter, C. and J. Robinson. 1967. Pharmacodynamics of dieldrin (HEOD). I. Ingestion by human subjects for 18 months. *Arch. Environ. Health* 15:614-626.

Hunter, C. and J. Robinson. 1969. Pharmacodynamics of dieldrin (HEOD) ingestion by human subjects for 18 to 24 months, and postexposure for 8 months. *Arch. Environ. Health* 18:12-21.

Loose, L.D. 1982. Macrophage induction of T-suppressor cells in pesticide-exposed and protozoan-infected mice. *Environ. Health Perspect.* 43:89-97.

Loose, L.D., J.B. Silkworth and T. Charbonneau. 1981. Environmental chemical induced macrophage dysfunction. *Environ. Health Perspect.* 39:79-92.

Iatropoulos, M., A. Milling, W. Miller, G. Nohynek, K. Rozman, F. Coulston and F. Korte. 1975. Absorption, transport, and organotropism of dichlorobiphenyl (DCB), dieldrin, and hexachlorobenzene (HCB) in rats. *Environ. Res.* 10:384-389.

National Cancer Institute (NCI). 1978. *Bioassay of aldrin and dieldrin for possible carcinogenicity*. DHEW Publication No. (NIH) 78-821. Technical Report Series No. 21.

Ottolenghi, A., J. Haseman and F. Suggs. 1974. Teratogenic effects of aldrin, dieldrin, and endrin in hamsters and mice. *Teratology* 9:11-16.

Probst, G., R. McMahon, L. Hill, D. Thompson, J. Epp and S. Neal. 1981. Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 chemicals. *Environ. Mutagenesis* 3:11-32.

Shell. 1984. *Review of mammalian and human toxicology, aldrin and dieldrin*. Review series HSE 84.003. Shell International Petroleum Maatschappij. B.V. The Hague.

Sundaram, K., V. Damodaran and T. Venkitasubramanian. 1978a. Absorption of dieldrin through monkey and dog skin. *Indian J. Exp. Biol.* 16:101-103.

Sundaram, K., V. Damodaran and T. Venkitasubramanian. 1978b. Absorption of dieldrin through skin. *Indian J. Exp. Biol.* 16:1004-1007.

Treon, J. and F. Cleveland. 1955. Toxicity of certain chlorinated hydrogen insecticides for laboratory animals, with special reference to aldrin and dieldrin. *Agric. Food Chem.* 3:402-408.

U.S. Environmental Protection Agency (USEPA). 1988. *Chemical profiles for extremely hazardous substances. Aldrin*. June 1988.

Walker, A., D. Stevenson, J. Robinson, E. Thorpe and M. Roberts. 1969. The toxicology and pharmacodynamics of dieldrin (HEOD): Two-year oral exposures of rats and dogs. *Toxicol. Appl. Pharmacol.* 15:345-373.

Dioxins

The general population is primarily exposed to dioxins through inhalation of air which has been contaminated by a variety of combustion sources; dioxins has been identified in tobacco smoke. Exposure may also occur through consumption of contaminated food and drinking water. Occupational exposure can occur through inhalation and dermal contact, particularly at sites engaged in combustion/carbonization processes such as coal tar and coal gasification operations.

TCDD is a probable human carcinogen. It has been most strongly linked with soft tissue sarcomas. More limited evidence suggests associations with several other cancers. In a new US EPA re-assessment, the upper limit for overall cancer risk for the general population may be as high as 1:1000. Dioxins may be human teratogens, specifically for ectodermal dysplasia and CNS, cardiac and skeletal defects.

Little is known about potential human health effects (if any) of long-term exposure to low concentrations. The US EPA considers dioxin (TCDD) to be probably carcinogenic to humans (group B2).

Osborne-Mendel rats (50/sex/dose) and B6C3F1 mice (50/sex/dose) were gavaged with the hexa-chlorodibenzo-p-dioxin mixture suspended in a 9:1 corn oil: acetone vehicle (NTP, 1980a). Treatment was twice weekly for 104 weeks at doses of 0, 1.25, 2.5 or 5.0 ug/kg/week for rats and male mice and 0, 2.5, 5 or 10 ug/kg/week for female mice. There were 75 each rats and mice of each sex as vehicle controls and 25 each female and male rats and mice in the untreated control group. A dose-related depression in mean body weight gain was noted in male and female rats. In rats and mice there was a dose-related toxic hepatitis consisting of degenerative liver changes and necrosis. A significant dose-related increase in incidence of hepatocellular carcinomas or neoplastic nodules was noted in male rats. NTP concluded that evidence for carcinogenicity in male rats was inconclusive. Incidence of hepatocellular carcinomas, nodules, and adenomas was significantly increased in female rats relative to vehicle controls both medium- and high-dose). Incidence of hepatocellular carcinomas and adenomas was increased in a dose-related manner in male and female mice, reaching statistical significance when the high-dose males were compared with vehicle controls.

Thirty Swiss-Webster mice/sex were skin-painted with a 2:1 mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin in acetone 3 times a week for 104 weeks (NTP, 1980b). Doses of 0.005 ug/application for the initial 16 weeks were followed by a 0.01 ug/application for the remainder of the study. No carcinogenic response related to treatment was observed.

TCDD is not directly genotoxic, but the TCDD-Ah receptor complex can bind to specific DNA enhancer sequences. This induces a pleiotropic sequence of genetic expression whose products may activate pro-mutagens. The US EPA has been re-evaluating the health effects of dioxins for the past several years and is expected to issue a final report in 1995. This report is expected to conclude that TCDD is a probable human carcinogen for soft tissue sarcomas and is a likely human reproductive hazard.

Rumack BH: POISINDEX(R) Information System. Micromedex Inc., Englewood, CO, 1995; *CCIS CD-ROM Volume 87*, edition exp Feb, 1996.

Hall AH & Rumack BH (Eds): TOMES(R) Information System. Micromedex, Inc., Englewood, CO, 1995; *CCIS CD-ROM Volume 87*, edition exp Feb, 1996.

NTP (National Toxicology Program). 1980a. Bioassay of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin (gavage) for possible carcinogenicity. DHHS Publ. No. (NIH) 80-1754.

NTP (National Toxicology Program). 1980b. Bioassay of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin (dermal study) for possible carcinogenicity. DHHS Publ. No. (NIH) 80-1758.

U.S. EPA. 1985. Health Assessment Document for Polychlorinated Dibenzo-p-dioxin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Air Quality Planning and Standards, Washington, DC. EPA 600/8/84-014F.

Heptachlor Epoxide

Heptachlor epoxide is a contaminant and metabolite of the insecticide, heptachlor. Heptachlor is readily absorbed from the gastrointestinal tract following oral exposure (ATSDR, 1997). Acute symptoms due to heptachlor exposure in humans include irritability, excessive salivation, labored respiration, muscle tremors, and convulsions (USEPA, 1987). Acute exposure of animals to heptachlor and heptachlor epoxide produced tremors, convulsions, paralysis, and hypothermia (USEPA, 1985). Chronic exposure of experimental animals to dietary concentrations of heptachlor or heptachlor epoxide has been associated with increased liver weight and hepatocellular carcinoma; heptachlor also induced hepatic lesions (USEPA, 1987; Velsicol, 1955; Dow Chemical, 1955; Davis, 1965; Epstein, 1976; NCI, 1977; Velsicol, 1973). In the presence of metabolic activation, both heptachlor and heptachlor epoxide induced unscheduled DNA synthesis in transformed human fibroblasts (Ahmed *et al.*, 1977). Heptachlor also increased the frequency of chromosomal aberrations in bone marrow cells of mice (Markarjan, 1966). Results of studies with rodents also indicate that heptachlor epoxide induces reproductive and developmental effects (USEPA, 1987).

Heptachlor epoxide is classified as Group B2 - Probable Human Carcinogens based on sufficient evidence of carcinogenicity in animal studies and inadequate evidence of carcinogenicity in humans. Using the geometric mean of potency factors from four separate experiments in which mice exposed to dietary concentrations of heptachlor epoxide exhibited hepatocellular carcinomas (Davis, 1965; NCI, 1977; Velsicol, 1973), USEPA estimated an oral cancer slope factor for heptachlor epoxide of $9.1 \text{ (mg/kg-day)}^{-1}$. An oral RfD, based on chronic systemic toxicity, has also been calculated for heptachlor epoxide. In a Dow Chemical study (1958), beagle dogs of both sexes fed heptachlor epoxide in their diet for 60 weeks developed increased liver-to-body weight ratios. No NOEL was determined from this study, but a LOEL of 0.5 ppm (0.0125 mg/kg-day) was identified from the available data. An oral RfD of $1.3 \times 10^{-5} \text{ mg/kg-day}$ for heptachlor epoxide was estimated from these data by applying an uncertainty factor of 1,000 to the LOEL.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for heptachlor/heptachlor epoxide*. U.S. Public Health Service.

Ahmed, F.E., R.W. Hart and J.J. Lewis. 1977. Pesticide induced DNA damage and its repair in cultured human cells. *Mutat. Res.* 42:116-174.

Davis, K. 1965. *Pathology Report on mice fed aldrin, dieldrin, heptachlor and heptachlor epoxide for two years*. Internal FDA memorandum to Dr. A.J. Lehman; July 19, 1965.

Dow Chemical Company (Dow Chemical). 1955. *60-Week feeding study with dogs*. MRID No. 00061912.

Epstein, S.S. 1976. Carcinogenicity of heptachlor and chlordane. *Sci. Total Environ.* 6:103.

Markarjan, D.S. 1966. Cytogenetic effect of some chlororganic insecticides on the nuclei of mouse bone-marrow cells. *Genetika* 1:132-137.

National Cancer Institute (NCI). 1977. *Bioassay of heptachlor for possible carcinogenicity*. Technical Report Series No. 9.

U.S. Environmental Protection Agency (USEPA). 1985. *Drinking water criteria document for heptachlor, heptachlor epoxide and chlordane*. Final draft. PB86-117991 EPA 600/X. March 1985.

U.S. Environmental Protection Agency (USEPA). 1987. *Health effects assessment for heptachlor*. Final draft. Environmental Criteria and Assessment Office. ECAO-CIN H085.

Velsicol Chemical Corporation (Velsicol). 1955. *2-Year feeding study with rats*. MRID No. 00062599.

Velsicol Chemical Corporation (Velsicol). 1973. MRID No. 00062678.

Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are complex mixtures of chlorinated biphenyls. There are 209 individual PCB congeners which comprise environmental and commercial mixtures of PCBs to varying degrees. The commercial PCB mixtures that were manufactured in the United States were given the trade name of "Aroclor." Aroclors are distinguished by a four-digit number (for example, Aroclor-1260). The last two digits in the Aroclor 1200 series represent the average percentage by weight of chlorine in the product. Each Aroclor contains numerous congeners; for example, Aroclor-1260 contains 80 individual congeners when analyzed by high resolution chromatography (Safe *et al.*, 1987). Not all of the congeners are equally toxic. In general, coplaner PCB molecules which are sterically similar to 2,3,7,8-tetrachloro-dibenzodioxin (TCDD) (3,3',4,4',5-penta-CB, 3,3',4,4',5,5'-hexa-CB and 3,3',4,4'-tetra-CB), exhibit the highest toxicity in laboratory animals (Kamrin and Fischer, 1991). The toxicity of an environmental mixture of PCBs will largely be determined by the quantities of the highly toxic congeners that are present in the mixture.

PCBs in pure form are readily and extensively absorbed through the gastrointestinal tract and somewhat less readily through the skin; PCBs are presumably readily absorbed from the lungs, but few data are available that experimentally define the extent of absorption after inhalation (USEPA, 1985). Studies have found oral absorption efficiency on the order of 75% to >90% in rats, monkeys and ferrets (Albro and Fishbein, 1972; Allen *et al.*, 1974; Tanabe *et al.*, 1981; Bleavens *et al.*, 1984; Clevenger *et al.*, 1989). PCBs distribute preferentially to adipose tissue and concentrate in human breast milk due to its high fat content (ATSDR, 1997). The binding of PCBs to a soil or sediment matrix inhibits absorption by all routes (ATSDR, 1997).

Dermatitis and chloracne (a disfiguring and long-term skin disease) have been the most prominent and consistent findings in studies of occupational exposure to PCBs. Several studies examining liver function in exposed humans have reported disturbances in blood levels of liver enzymes. Reduced birth weights, slow weight gain, reduced gestational ages, and behavioral deficits in infants were reported in a study of women who had consumed PCB-contaminated fish from Lake Michigan (USEPA, 1985). Reproductive, developmental, hepatic, immunotoxic, and

immunosuppressive effects appear to be the most sensitive end points of PCB toxicity in nonrodent species, and the liver appears to be the most sensitive target organ for toxicity in rodents (USEPA, 1985). For example, adult monkeys exposed to dietary concentrations of 0.028 mg/kg-day Aroclor-1016 for approximately 22 months showed no evidence of overt toxicity; however, the offspring of these monkeys exhibited decreased birth weight and possible neurological impairment (Barsotti and Van Miller, 1984; Levin *et al.*, 1988; Schantz *et al.*, 1989, 1991).

A number of studies have suggested that PCB mixtures are capable of increasing the frequency of tumors including liver tumors in animals exposed to the mixtures for long periods (Kimbrough *et al.*, 1975; NCI, 1978; Schaeffer *et al.*, 1984; Norback and Weltman, 1985). In addition, studies have suggested that PCB mixtures can act to promote or inhibit the action of other carcinogens in rats and mice (USEPA, 1985). It is known that PCB congeners vary greatly in their potency in producing biological effects, such as cancer; however, USEPA generally considers Aroclor-1260 to be the Aroclor with the greatest tumorigenic potential and, therefore, conservatively uses this Aroclor to be representative of all PCB mixtures for the evaluation of carcinogenic effects. Nevertheless, USEPA has acknowledged that there is some evidence that mixtures containing highly chlorinated biphenyls are more potent inducers of hepatocellular carcinoma in rats than are mixtures containing less chlorine by weight following oral exposure. The responses are mostly limited to the livers in rats and mice, although there is a suggestion that some PCB mixtures may also affect the stomach of rats and monkeys (Chase *et al.*, 1989). Statistically significant increases in malignant tumors have not been observed in animal studies with PCB mixture containing less than 60 percent chlorine content (Chase *et al.*, 1989). There is some suggestive evidence that Aroclor-1254 induces hepatocellular adenomas and carcinomas combined in male rats based on the reclassification and reevaluation of the NCI (1978) tumor data conducted by Ward (1985). However, the majority of tumors were benign (statistically significant alone), while the few malignant tumors (carcinomas) were not statistically elevated by themselves. At present, there is uncertainty as to whether or not Aroclor-1248, -1242, or -1232 are tumorigenic in animals. This is because there are no valid cancer bioassays for these mixtures (Chase *et al.*, 1989).

Existing epidemiological data do not indicate a consistent tumorigenic effect among individuals exposed to PCBs. ATSDR (1997) concluded that occupational studies involving predominantly inhalation and dermal exposures to PCBs have suggested an association between the development of liver, gastrointestinal, hematopoietic and skin cancer and PCB exposure. However, the majority of these studies were mortality studies that reported nonstatistically significant results, were confounded by concurrent exposure to other chemicals (many of which are considered to be potential carcinogens), had small sample sizes or number of deaths, or unquantified PCBs exposures. In addition, there is no consistent pattern of associations among the various studies, either with respect to type of human cancers observed or the nature and extent of PCB exposures.

USEPA classifies PCBs as Group B2 - Probable Human Carcinogens based on sufficient evidence in animal bioassays and inadequate evidence from studies in humans. USEPA recently revised the oral slope factor for PCBs to multiple possible slope factors corresponding to three different tiers. The appropriate tier for used depends on the level of risk and likely persistence of the congeners evaluated. The top tier, for "high risk and persistence," is considered most appropriate at this site. The criteria for use of this tier, suggested by USEPA, are as follows: (1)

food chain exposures; (2) sediment or soil ingestion; (3) dust or aerosol inhalation; (4) dermal exposure, if an absorption factor has been applied; (5) presence of dioxin-like, tumor-promoting, or persistent congeners; and (6) early-life exposures. The upper-bound slope factor, to be used for RME risk estimates, is 2.0 (mg/kg-day)⁻¹ and the central-estimate slope factor, for central tendency risk estimates, is 1.0 (mg/kg-day)⁻¹. Dose-response data were generated based on the incidence of liver hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas in female Sprague-Dawley rats exposed to Aroclor-1260, -1254, -1242, and -1016 separately in one study (Brunner *et al.*, 1996) and only Aroclor-1260 in another study (Norback and Weltman, 1985). USEPA derived an oral RfD of 2×10^{-5} mg/kg-day for Aroclor-1254 based on a 55-month oral study conducted in monkeys (Arnold *et al.*, 1993a,b; Tryphonas *et al.*, 1989, 1991a,b). A LOAEL of 0.005 mg/kg-day was observed, and significant effects were observed including immunological system effects, ocular exudate, inflamed Meibomian glands, and distorted growth of finger and toe nails. An uncertainty factor of 300 was used to calculate the RfD.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for polychlorinated biphenyls*. U.S. Public Health Service.

Albro, P.W. and L. Fishbein. 1972. Intestinal absorption of polychlorinated biphenyls in rats. *Bull. Environ. Contam. Toxicol.* 8:26-31.

Allen, J.R., D.H. Norback and I.C. Hsu. 1974. Tissue modifications in monkeys as related to absorption, distribution, and excretion of polychlorinated biphenyls. *Arch. Environ. Contam. Toxicol.* 2:86-95.

Arnold, D.L., F. Bryce and R. Stapley. 1993a. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (*Macaca mulatta*) monkeys, Part 1A: Prebreeding phase - clinical health findings. *Food Chem. Toxicol.* 31:799-810.

Arnold, D.L., F. Bryce and K. Karpinski. 1993b. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (*Macaca mulatta*) monkeys, Part 1B: Prebreeding phase -clinical and analytical laboratory findings. *Food Chem. Toxicol.* 31: 811-824.

Barsotti, D.A. and J.P. Van Miller. 1984. Accumulation of a commercial polychlorinated biphenyl mixture (Aroclor 1016) in adult rhesus monkeys and their nursing infants. *Toxicology* 30:31-44.

Bleavins, M.R., W.J. Breslin and R.J. Aulerich. 1984. Placental and mammary transfer of a polychlorinated biphenyl mixture (Aroclor 1254) in the European ferret (*Mustela putorius furo*). *Environ. Toxicol. Chem.* 3:637-644.

Brunner, M.J., T.M. Sullivan and A.W. Singer. 1996. *An assessment of the chronic toxicity and oncogenicity of Aroclor-1016, Aroclor-1242, Aroclor-1254, and Aroclor-1260 administered in diet to rats*. Study No. SC920192. Chronic toxicity and oncogenicity report. Battelle, Columbus, OH.

Chase, K., J. Doull, S. Friess, J. Rodericks and S. Safe. 1989. *Evaluation of the toxicology of PCBs*. Prepared for Texas Eastern Gas Pipeline Company. March 1989.

Clevenger, M.A., S.M. Roberts and D.L. Lattin. 1989. The pharmacokinetics of 2,2',5,5'-tetrachlorobiphenyl and 3,3',4,4'-tetrachlorobiphenyl and its relationship to toxicity. *Toxicol. Appl. Pharmacol.* 100:315-327.

Kamrin, M.P. and L.J. Fischer. 1991. Workshop of human health impacts of halogenated biphenyls and related compounds. *Environ. Health Perspect.* 91:157-164.

Kimbrough, R.D., R.A. Squire, R.E. Linder, J.D. Strandberg, R.J. Montali and V.W. Burse. 1975. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. *J. Natl. Cancer Inst.* 55:1453.

Levin, E.D., S.L. Schantz and R.E. Bowman. 1988. Delayed spatial alteration deficits resulting from perinatal PCB exposure in monkeys. *Arch. Toxicol.* 62:267-273.

National Cancer Institute (NCI). 1978. *Bioassay of Aroclor 1254 for possible carcinogenicity*. Cas. No. 27323-18-8. Technical Report Series No. 38. DHEW (NIH) Publication No. 78-838.

Norback, D.H. and R.H. Weltman. 1985. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. *Environ. Health Perspect.* 1:134-143.

Safe, S., L. Safe and M. Mullin. 1987. *Polychlorinated biphenyls*. *Environ. Toxin Series: Vol. I*. Berlin: Springer Verlag.

Schaeffer, E., H. Greim and W. Goessner. 1984. Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. *Toxicol. Appl. Pharmacol.* 75:278-288.

Schantz, S.L., E.D. Levin and R.E. Bowman. 1989. Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys. *Neurotoxicol. Teratol.* 11:243-250.

Schantz, S.L., E.D. Levin and R.E. Bowman. 1991. Long-term neurobehavioral effects of perinatal polychlorinated biphenyl (PCB) exposure in monkeys. *Environ. Toxicol. Chem.* 10:747-756.

Tanabe, S., Y. Nakagawa and R. Tatsukawa. 1981. Absorption efficiency and biological half-life of individual chlorobiphenyls in rats treated with kanechlor products. *Agric. Biol. Chem.* 45:717-726.

Tryphonas, H., S. Hayward and L. O'Grady. 1989. Immunotoxicity studies of PCB (Aroclor 1254) in the adult rhesus (*Macaca mulatta*) monkey — preliminary report. *Int. J. Immunopharmacol.* 11:199-206.

Tryphonas, H., M.I. Luster and G. Schiffman. 1991a. Effect of chronic exposure of PCB (Aroclor 1254) on specific and nonspecific immune parameters in the rhesus (*Macaca mulatta*) monkey. *Fundam. Appl. Toxicol.* 16:773-786.

Tryphonas, H., M.I. Luster and K.L. White. 1991b. Effects of PCB (Aroclor 1254) on non-specific immune parameters in Rhesus (*Macaca mulatta*) monkeys. *Int. J. Immunopharmacol.* 13:639-648.

U.S. Environmental Protection Agency (USEPA). 1985. *Health effects criteria document on polychlorinated biphenyls. Final draft.* Office of Drinking Water.

Ward, J. 1985. Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Aroclor 1254. *Environ. Health Perspect.* 60:89-95.

INORGANICS

Antimony

Antimony is a metal which occurs both in the trivalent and pentavalent oxidation states (USEPA, 1980). Absorption of this metal via oral routes of exposure is low (10% for antimony, tartrate; 1% for all other forms) (ATSDR, 1997). Organic antimony is more toxic than the inorganic compounds due to increased absorption. Humans and animals exposed acutely by oral or inhalation exposures to either the trivalent or pentavalent forms of antimony displayed electrocardiogram (ECG) changes and myocardial lesions (USEPA, 1980). Pneumoconiosis has been observed in humans exposed by acute inhalation and dermatitis has occurred in individuals exposed either orally or dermally. Following acute oral exposure to antimony trioxide or potassium antimony tartrate, both humans and laboratory animals (dogs) manifested nausea and vomiting (ATSDR, 1997). Humans and laboratory animals (i.e., rat and pig) chronically exposed to antimony compounds (antimony trioxide, pentoxide, and trisulfide) via inhalation manifested respiratory effects including macrophage proliferation, fibrosis and pneumonia at LOAELs ranging from 0.046 to 86.3 mg/m³ (ATSDR, 1997). Chronic oral exposure in rats (0.35 mg/kg-day) resulted in altered blood glucose and blood cholesterol levels and decreased lifespan (Schroeder *et al.*, 1970). A single report (Balyeava, 1967) noted an increase in spontaneous abortions, premature births, and gynecological problems in 318 female workers exposed to a mixture of antimony metal, antimony trioxide, and antimony pentasulfide dusts. No change in the incidence of cancer was observed in laboratory animals (i.e., rats, mice) fed 0.262 or 0.35 mg/kg-day antimony as potassium antimony tartrate for a lifetime.

USEPA derived a chronic oral RfD of 4×10^{-4} mg/kg-day for antimony (as potassium antimony tartrate) based on a chronic oral study (Schroeder *et al.*, 1970) in which rats given the metal in drinking water had altered blood glucose and blood cholesterol levels and decreased lifespan. An uncertainty factor of 1,000 and a LOAEL of 0.35 mg/kg-day were used to derive the oral RfD.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for antimony.* U.S. Public Health Service.

Balyaeva, A.P. 1967. The effects of antimony on reproduction. *Gig. Truda Prof. Zabol.* 11:32.

Schroeder, H.A., M. Mitchner and A.P. Nasor. 1970. Zirconium, niobium, antimony, vanadium, and lead in rats: Life-term studies. *J. Nutr.* 4100:59-66.

U.S. Environmental Protection Agency (USEPA). 1980. *Ambient water quality criteria for antimony.* Office of Water Regulations and Standards.

Arsenic

Arsenic is difficult to characterize as a single analyte because it has complex chemistry. It may be trivalent or pentavalent and is widely distributed in nature (ATSDR, 1997). Both inorganic and organic forms of arsenic are readily absorbed via oral and inhalation routes. Soluble forms are more readily absorbed than insoluble forms (USEPA, 1984). Approximately 95% of soluble inorganic arsenic administered to rats is absorbed from the gastrointestinal tract (Coulson *et al.*, 1935; Ray-Bettley and O'Shea, 1975). Approximately 70–80% of arsenic deposited in the respiratory tract of humans has been shown to be absorbed (Holland *et al.*, 1959). Dermal absorption is not significant (USEPA, 1984). At mining sites, arsenic is expected to occur in naturally occurring mineral assemblages with considerably lower bioavailability than expected in soluble inorganic arsenic salts (Davis *et al.*, 1992).

Acute exposure in humans by ingestion of metallic arsenic has been associated with gastrointestinal effects, hemolysis, and neuropathy (USEPA, 1984). Chronic human arsenicism (by drinking water ingestion) is associated with increased risk of nonmelanoma, typically nonlethal, skin cancer and a peripheral vascular disorder that results in gangrene of the extremities, especially feet, known as blackfoot disease (Tseng, 1977). Additionally, there is strong evidence to suggest ingested inorganic arsenic causes cancers of the bladder, kidney, lung, and liver, and possibly other sites (Bates *et al.*, 1992; Chen *et al.*, 1992; Chen *et al.*, 1986). It is well known that hyperpigmentation and keratosis are also associated with chronic arsenicism (Neubauer, 1947) and arsenic can produce toxic effects on both the peripheral and CNS, precancerous dermal lesions, and cardiovascular damage (USEPA, 1984; Tseng, 1977). Arsenic is embryotoxic, fetotoxic, and teratogenic in several animal species (USEPA, 1984). No evidence of reproductive toxicity was found (Calabrese and Kenyon, 1991). Epidemiological studies of workers in smelters and in plants manufacturing arsenical pesticides have shown inhalation of arsenic is strongly associated with lung cancer and less so, with hepatic angiosarcoma (USEPA, 1984).

There is substantial evidence that establishes the nutritional essentiality of trace levels of arsenic. Deficiency has been shown to depress growth and impair reproduction in rats, minipigs, chickens, and goats (USEPA, 1988; NRC, 1989). Methylation of arsenic to less toxic, more rapidly excreted chemical species provides an effective detoxification mechanism *in vivo*. In humans, this system may become saturated at daily oral intake rates greater than 250–1,000 $\mu\text{g}/\text{day}$. For this reason, the dose-response curve for arsenic, for carcinogenicity and systemic toxicity, may have nonlinearities, i.e., a portion of the dose-response curve exists over which increases in dose do not result in comparable increases in physiological response (Petito and Beck, 1990).

USEPA classified arsenic as Group A - Human Carcinogen. USEPA derived an oral cancer slope factor of $1.5 \text{ (mg/kg-day)}^{-1}$ based on two epidemiological studies (Tseng *et al.*, 1968; Tseng, 1977) which indicated an increased incidence of skin cancer in individuals exposed to arsenic in drinking water. A chronic oral RfD of $3 \times 10^{-4} \text{ mg/kg-day}$ was calculated for arsenic based on incidence of keratosis and hyperpigmentation in humans (Tseng, 1977). An uncertainty factor of 3 and a modifying factor of 1 were used to derive the chronic oral RfD. Applying USEPA's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the recommended RfD (i.e., 0.1–0.8 $\mu\text{g/kg-day}$).

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for arsenic*. U.S. Public Health Service.

Bates, M.N., A.H. Smith and C. Hopenhayn-Rich. 1992. Arsenic ingestion and internal cancers: a review. *Am. J. Epidemiol.* 135:462-476.

Calabrese, E.J. and E.M. Kenyon. 1991. *Air toxics and risk assessment*. Chelsea, MI: Lewis Publishers, Inc.

Chen, C-J., C-W. Chen, M-M. Wu and T-L. Kuo. 1992. Cancer potential in liver, lung, bladder, and kidney due to ingested inorganic arsenic in drinking water. *Br. J. Cancer* 66:888-892.

Chen, C-J., Y. Chuang, S. You, T. Lin and H. Wu. 1986. A retrospective study on malignant neoplasms of bladder, lung, and liver in blackfoot disease endemic area in Taiwan. *Br. J. Cancer* 53:399-405.

Coulson, E.J., R.E. Remington and K.M. Lynch. 1935. Metabolism in the rat of the naturally occurring arsenic of shrimp as compared with arsenic trioxide. *J. Nutr.* 10:255-270.

Davis, A., M.V. Ruby and P.D. Bergstrom. 1992. Bioavailability of arsenic and lead in soils from the Butte, Montana Mining District. *Environ. Sci. Technol.* 26:461-468.

Holland, R.H., M.S. McCall and H.C. Lanz. 1959. A study of inhaled arsenic-74 in man. *Cancer Res.* 19:1154-1156.

National Research Council (NRC). 1989. *Recommended dietary allowances*. National Academy Press.

Neubauer, O. 1947. Arsenical cancer — a review. *Br. J. Cancer* 1:192.

Petito, C.T. and B.D. Beck. 1990. Evaluation of evidence of nonlinearities in the dose-response curve for arsenic carcinogenesis. *Trace Sub. Environ. Health* 24:143-176.

Ray-Bettley, F. and J.A. O'Shea. 1975. The absorption of arsenic and its relation to carcinoma. *Br. J. Dermatol.* 92:563-568.

Tseng, W.P. 1977. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. *Environ. Health Perspect.* 19:109-119.

Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin and S. Yen. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J. Natl. Cancer Inst.* 40:453-463.

U.S. Environmental Protection Agency (USEPA). 1984. *Health assessment document for inorganic arsenic.* Office of Health and Environmental Assessment. EPA 600/8-83-021F.

U.S. Environmental Protection Agency (USEPA). 1988. *Special report on ingested inorganic arsenic skin cancer: nutritional essentiality.* EPA/625/3-87/013F. July 1988.

Barium

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. 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/m³ 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/m³ of barium carbonate. Similar results were obtained with female rats treated with 13.4 mg barium carbonate/m³. The NOAEL for developmental effects was 1.15 mg/m³ (equivalent to 0.8 mg barium/m³). An inhalation reference concentration (RfC) of 0.005 mg/m³ for subchronic and 0.0005 mg/m³ for chronic exposure was calculated by the EPA based on the NOAEL for developmental effects. 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

Brenniman, G. R. and P. S. Levy. 1984. High barium levels in public drinking water and its association with elevated blood pressure. In: *Advances in Modern Toxicology IX*, E. J. Calabrese, Ed. Princeton Scientific Publications, Princeton, NJ. pp. 231-249.

Perry, H. M., S. J. Kopp, M. W. Erlanger, and E. F. Perry. 1983. Cardiovascular effects of chronic barium ingestion. In: *Trace Substances in Environmental Health*, XVII, D. D. Hemphill, ed. Proc. Univ. Missouri's 17th Ann. Conf. on Trace Substances in Environmental Health. University of Missouri Press, Columbia, MO. pp. 155-164.

Tarasenko, M, O. Promin, and A. Silayev. 1977. Barium compounds as industrial poisons (an experimental study). *J. Hyg. Epidem. Microbiol. Immunol.* 21:361-373.

Wones, R. G., B. L. Stadler, and L. A. Frohman. 1990. Lack of effect of drinking water barium on cardiovascular risk factor. *Environ. Health Perspect.* 85:1-13.

Cadmium

Gastrointestinal absorption of cadmium in humans ranges from 5 to 6% (USEPA, 1985a). Based on a comprehensive model for inhaled cadmium, the deposition rate of particulate airborne cadmium is 5-50% (i.e., 5% of particles greater than 10 microns and up to 50% of particles less than 0.1 microns), and 50-100% of the cadmium deposited was absorbed (Nordberg *et al.*, 1985). Cadmium bioaccumulates in humans, particularly in the kidney and liver (USEPA, 1985a,b). Acute oral exposure to cadmium in laboratory animals resulted in systemic, immunological, neurological, developmental, and reproductive effects at doses of 2-138 mg/kg-day (ATSDR, 1997). Chronic oral or inhalation exposure of humans to cadmium has been associated with renal dysfunction, itai-itai disease (bone damage), hypertension, anemia, endocrine alterations, and immunosuppression. Renal toxicity occurs in humans chronically exposed to cadmium in food at LOAEL of 0.0075 mg/kg-day. In laboratory animals (i.e., rat, mouse) chronic oral exposure to cadmium results in increased blood pressure, hematological, and renal effects at LOAELs ranging from 0.014 to 57 mg/kg-day (ATSDR, 1997). Teratogenic and reproductive effects (i.e., decreased fetal and birth weight, delayed ossification, behavioral impairment, and reduced fertility) were reported in laboratory animals (i.e., rat, mice, dogs) subchronically exposed to cadmium in drinking water at LOAELs ranging from 0.04 to 40 mg/kg-day (ATSDR, 1997). Epidemiological studies have demonstrated a strong association between inhalation exposure to cadmium and cancers of the lung, kidney, and prostate (USEPA, 1985b; Thun *et al.*, 1985). In experimental animals, cadmium induces injection-site sarcomas

and testicular tumors. When administered by inhalation, cadmium chloride is a potent pulmonary carcinogen in rats. Cadmium is a well-documented animal teratogen (USEPA, 1985b).

USEPA classified cadmium as Group B1 - Probable Human Carcinogen by inhalation. This classification applies to agents for which there is limited evidence of carcinogenicity in humans from epidemiologic studies. Using renal toxicity as an endpoint, and a safety factor of 10, USEPA derived two separate oral RfDs. The RfD associated with oral exposure to drinking water is 5×10^{-4} mg/kg-day, and is based on the LOAEL of 0.005 mg/kg in humans (USEPA, 1985a; Friberg *et al.*, 1974). The RfD associated with exposure to cadmium in food is 1×10^{-3} mg/kg-day.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for cadmium*. U.S. Public Health Service.

Friberg, L., M. Piscator, G.F. Nordberg and T. Kjellstrom. 1974. *Cadmium in the environment*, 2nd ed. Boca Raton, FL: CRC Press, Inc.

Nordberg, G.F., T. Kjellstrom and M. Nordberg. 1985. Kinetics and metabolism. In: *Cadmium and health: A toxicological and epidemiological appraisal. Vol I. Exposure, dose, and metabolism*, eds. L. Friberg, C.G. Elinder, T. Kjellstrom, et al. Boca Raton, FL: CRC Press. pp. 103-178.

Thun, M.J., T.M. Schnorr, A.B. Smith, W.E. Halperin and B.A. Lemen. 1985. Mortality among a cohort of U.S. cadmium production workers—an update. *J. Natl. Cancer Inst.* 74:325-333.

U.S. Environmental Protection Agency (USEPA). 1985a. *Drinking water criteria document for cadmium. Final draft*. Office of Drinking Water. PB86-117934. April 1985.

U.S. Environmental Protection Agency (USEPA). 1985b. *Updated mutagenicity and carcinogenicity assessment of cadmium. Addendum to the health assessment document for cadmium (May 1981; EPA/600/8-81/023)*. Office of Health and Environmental Assessment. EPA 600/8-83-025F. June 1985.

Chromium

Chromium exists in two states, as chromium (III) and as chromium (VI). Following oral exposure, absorption of chromium (III) has been reported to be 0.4% while absorption of chromium (VI) has been observed to be as high as 10% (ATSDR, 1997). However, chromium (VI) is rapidly reduced to chromium (III) after penetration of biological membranes and in the gastric environment (ATSDR, 1997). Chromium is an essential micronutrient and is not toxic in trace quantities (USEPA, 1980). Alterations in liver enzyme activities were noted in rats administered an oral dose of 13.5 mg/kg-day chromium (VI) for 20 days (Kumar *et al.*, 1985). Rats subchronically administered higher concentrations of chromium VI (98 mg/kg-day) have exhibited adverse effects on renal function (Diaz-Mayans *et al.*, 1986). No significant changes, however, were detected in the livers or kidneys of rats exposed to 2.7 mg/kg-day or 3.5 mg/kg-

day chromium (III) or chromium (VI), respectively, in the drinking water for 1 year (MacKenzie *et al.*, 1958; ATSDR, 1997). CNS effects including hypoactivity have been reported in rats when exposed to subchronic levels of 98 mg/kg-day chromium VI in drinking water (Diaz-Mayans *et al.*, 1986). Workers exposed to 2 $\mu\text{g}/\text{m}^3$ chromic acid vapors (mean duration of 2.5 years), a soluble chromium (VI) compound, exhibited atrophy and ulceration of the nasal mucosa and transient decrease in lung function (Lindberg and Hedenstierna, 1983). There is, however, insufficient scientific evidence that chromium (III) compounds by themselves elicit atrophy of the nasal mucosa or adverse respiratory effects in humans (ATSDR, 1997). Furthermore, epidemiological studies of worker populations have clearly established that inhaled chromium (VI) is a human carcinogen; the respiratory passages and the lungs are the target organs (Mancuso, 1975; USEPA, 1984). Inhalation of chromium (III) or ingestion of chromium (VI) or (III) has not been associated with carcinogenicity in humans or experimental animals (USEPA, 1984). Oral exposure of pregnant mice (gestational days, 1 to 19) to 57 mg/kg-day chromium (VI) resulted in embryo-lethal effects (e.g., increased resorptions and postimplantation loss), reduced ossification and gross anomalies (Trivedi *et al.*, 1989). Chromium (III) does not appear to cause fetotoxic or teratogenic effects in rats (ATSDR, 1997). Reproductive effects in the form of decreased sperm count were noted in mice administered oral doses of 4.6 mg/kg-day chromium (VI) (225 ppm) and 3.5 mg/kg-day chromium (III) (172 ppm) for 7 weeks (Zahid *et al.*, 1990).

USEPA classified inhaled chromium (VI) in Group A—Human Carcinogen by the inhalation route. Inhaled chromium (III) and ingested chromium (III) and (VI) have not been classified with respect to carcinogenicity. USEPA derived a chronic oral RfD of 5×10^{-3} mg/kg-day for chromium (VI) based on a study by MacKenzie *et al.* (1958) in which no adverse effects were observed in rats exposed to 2.4 mg chromium (VI)/kg-day in drinking water for 1 year. A safety factor of 500 was used to derive the RfD. USEPA developed an oral RfD of 1 mg/kg-day for chromium (III) based on a study in which rats were exposed to chromic oxide baked in bread. No effects due to chromic oxide treatment were observed at any dose level (Ivankovic and Preussman, 1975); however, hepatotoxicity was the effect of concern. An uncertainty factor of 1,000 was used to calculate the RfD.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for chromium*. U.S. Public Health Service.

Diaz-Mayans, J., R. Laborda and A. Nunez. 1986. Hexavalent chromium effects on motor activity and some metabolic aspects of Wistar albino rats. *Comp. Biochem. Physiol.* 83:191-195.

Ivankovic, S. and R. Preussman. 1975. Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in subacute and long-term feeding experiments in rats. *Food Cosmet. Toxicol.* 13:347-351.

Kumar, A., S.V.S. Rana and R. Prakash. 1985. Dysenzymuria induced by hexavalent chromium. *Int. J. Tissue React.* 47:333-338.

Lindberg, E. and G. Hedenstierna. 1983. Chrome plating: Symptoms, findings in the upper airways, and effects on lung function. *Arch. Environ. Health* 38:367-374.

Mancuso, T.F. 1975. *International conference on heavy metals in the environment*. Toronto, Canada.

MacKenzie, R.D., R.V. Byerrum, C.F. Decker, C.A. Hoppert and F.L. Longham. 1958. Chronic toxicity studies II. Hexavalent and trivalent chromium administered in drinking water to rats. *Arch. Ind. Health* 18:232-234.

Trivedi, B., D.K. Saxena and R.C. Murphy. 1989. Embryotoxicity and fetotoxicity of orally administered hexavalent chromium in mice. *Reprod. Toxicol.* 3:275-278.

U.S. Environmental Protection Agency (USEPA). 1980. *Ambient water quality criteria for chromium*. Office of Water Regulations and Standards. EPA 440/5-80-035.

U.S. Environmental Protection Agency (USEPA). 1984. *Health assessment document for chromium*. Environmental Criteria and Assessment Office. EPA 600/8-83-014F.

Zahid, Z.R., Z.A. Al-Hakkak and A.H.H. Kadhim. 1990. Comparative effects of trivalent and hexavalent chromium on spermatogenesis of the mouse. *Toxicol. Environ. Chem.* 25:131-136.

Cyanide

Both cyanide gases and salts are used in industrial processes. Minor uses of HCN include insecticides and rodenticides for fumigating enclosed spaces (e.g., grain storage area). Cyanide salts are used mainly in the electroplating and metal-finishing industries. Minor applications of the salts include the manufacture of dyes and pigments, as well as use as insecticides and rodenticides (ATSDR, 1997).

Cyanide is readily absorbed following inhalation and oral exposure (see section on Relative Absorption Factors). Human and animal studies indicate cyanide is rapidly distributed by the blood following exposure (ATSDR, 1997). Metabolism involves (1) the conversion of cyanide to thiocyanate, (2) conversion to 2-aminothiazoline-4-carboxylic acid, (3) incorporation into a 1-carbon metabolic pool or (4) combining with hydroxycobalamin to form cyanocobalamin (ATSDR, 1989). Cyanide metabolites are excreted primarily in urine with small amounts eliminated through the lungs (ATSDR, 1997).

The fatal effects of exposure to high doses of cyanide over short periods of time are well known. Inhalation of 100 ppm HCN for 0.5 to 1 hour has been fatal to humans. Exposure to HCN vapors resulted in palpitations, shortness of breath, pain over the heart, vertigo, and involuntary eye movements (Carmelo, 1955), cyanosis, headache, altered EEG, and left-sided blindness (Sandberg, 1967). The cardiovascular effects are believed to be secondary to the CNS effects (ATSDR, 1997). HCN fumigators also exposed by inhalation and dermal contact developed palpitations, shortness of breath, pain over the heart, vertigo, and involuntary eye movements (Carmelo, 1955). The LD₅₀ in humans for ingestion exposure has been reported to be 1.5 mg/kg/day of CN⁻. A lower fatal dose in humans has been reported at 0.6 mg/kg/day CN⁻ (ATSDR, 1997). Brief exposure to lower levels of cyanide has resulted in rapid, deep breathing, shortness of breath, convulsions, and loss of consciousness. Because cyanide is not sequestered

in the body, these effects are reversible over time. However, longer-term exposure to these low levels has resulted in CNS, thyroid gland, and cardiovascular effects. Several occupational studies of workers exposed to HCN produced thyroid abnormalities. In a case-control study of electroplating workers exposed to 6.4 to 10.4 ppm HCN for 5 to 15 years, 56 percent of the exposed group had enlarged thyroid glands and significantly elevated hemoglobin levels and lymphocyte counts. It should be noted that these workers were also exposed to volatiles, there were varying exposure levels, and unmatched controls (El Ghawabi et al., 1975). Workers in a silver-reclaiming factory exposed an average of 10.5 months to a TWA of 16.6 mg/m³ HCN developed headache, dizziness, and mild thyroid abnormalities (Blanc et al., 1985). No studies of developmental effects in humans resulting from inhalation of cyanide are available.

When monkeys were exposed to 87 to 196 ppm HCN, severe disruptive changes in respiration and unconsciousness were noted (Purser et al., 1984). Tremors, convulsions, loss of equilibrium, dyspnea, nausea, exaggerated intestinal peristalsis, and diarrhea were noted in dogs exposed to 45 ppm HCN for varying durations (Valade, 1952). When rats were exposed to inhalation of HCN at low concentrations, cardiac enzyme changes resulted (O'Flaherty and Thomas, 1982). The previously cited Purser study of monkeys exposed to 87 to 196 ppm HCN from pyrolyzed polyacrylonitrile also found cardiovascular effects, including rapid induction of a semiconscious state and severe disruptive changes in respiration.

Male rats were fed 30 mg/kg/day cyanide for 11.5 months and developed vacuolization and myelin degeneration of the spinal cord (Philbrick et al., 1979). No CNS effects were reported by Howard and Hanzell (1955) for rats fed up to 10.8 mg/kg/day of CN-in HCN-fumigated feed for two years. Dogs fed 0.27 and 0.53 mg/kg/day cyanide in capsules for 16 weeks developed degenerative changes in the CNS ganglion cells, reduced ribonucleic acid (RNA) content, and inflammation (Hertting et al., 1960). Numerous studies of orally exposed pregnant animals have found maternal toxicities and developmental abnormalities in the offspring. Pregnant hamsters exposed to cyanide as D,L-amygdalin (a component of laetrile) exhibited maternal toxicity at 250 mg/kg and greater. Fetuses were examined at 15-days gestation, and dose-related abnormalities were observed in this group (Willhite, 1982). Female rats were fed a basal cassava diet containing 12 mg/kg HCN and a basal diet with 1.25 gm KCN per kg diet prior to mating, during gestation, and through lactation. The weanlings were subsequently fed these same diets. Those weanlings exposed to higher levels of cyanide in utero and during the post-weaning period had significantly decreased protein-efficiency ratios. Both the dams and weanlings fed the potassium cyanide enhanced diet had significantly increased serum thiocyanate levels (Tewe and Maner, 1981).

Cyanides have tested negative for mutagenicity and effects on DNA synthesis except for a study by Kushi et al. (1983) in which a marginally mutagenic response for HCN was reported. There are no data available indicating that cyanide has any carcinogenic effects (ATSDR, 1997).

Agency for Toxic Substances and Disease Registry (ATSDR) (1997) Toxicological profile for cyanide. U.S. Public Health Service.

Blanc, P., Hogan, M., Mallin, K., Hryhorczuk, D., Heassl, S. and Bernard, B. (1985) *Cyanide intoxication among silver reclaiming workers*. JAMA 253:367-371.

- Carmelo, S. (1955) *New contributions to the study of subacute-chronic hydrocyanic acid intoxication in men*. Ross. Med. Ind. 24:254-71.
- El Ghawabi, S.H., Gaafar, M.A., El-Saharti, A.A., Ahmed, S.H., Malash, K.K. and Fares, R. (1975) *Chronic cyanide exposure: A chemical radioisotope and laboratory study*. Brit. J. Ind. Med. 32:215-19.
- Hertting, G.O., Kraupp, E., Schnetz, E. and Wieketic, S.T. (1960) *Untersuchungen uber die folgen einer chronischen verabreichung akut toxischen dosen von natriumcyanide an hunden*. Acta Pharmacol. Toxicol. 17:27-43.
- Howard, J.W. and Hanzel, R.F. (1955) *Chronic toxicity for rats of food treated with hydrogen cyanide*. J. Agric. Food Chem. 3:325-29.
- Kushi, A., Matsumoto, T. and Yoshita, D. (1983) *Mutagen from the gaseous phase of protein pyrolyzate*. Agri. Biol. Chem. 47:1979-1982.
- Landahl, H.D. and Hermann, R.G. (1950) *Retention of vapors and gases in the human nose and lung*. Arch. Ind. Hyg. Occup. Med. 1:36-45.
- O'Flaherty, E.J. and Thomas, W.C. (1982) *The cardiotoxicity of hydrogen cyanide as a component of polymer pyrolysis smoke*. Toxicol. Appl. Pharmacol. 63:373-81.
- Philbrick, D.J. et al. (1979) *Effect of prolonged cyanide and thiocyanate feeding in rats*. J. Toxicol. Environ. Health. 5:579-592.
- Purser, A.W., Grimshaw, P. and Berrill, K.P. (1984) *Intoxication by cyanide in fires: A study in monkeys using polyacrylonitrile*. Arch. Environ. Health 39:394-400.
- Sandberg, C.G. (1967) *A case of chronic poisoning with potassium cyanide*. Acta Med. Scand. 18:233-36.
- Tewe, O.O. and Maner, J.H. (1981) *Long-term and carry-over effect of dietary inorganic cyanide (KCN) in the lifecycle performance and metabolism of rats*. Toxicol. Appl. Pharmacol. 58:1-7.
- Valade, M.P. (1952) *Injuries to the CNS in chronic experimental poisoning by hydrocyanic acid gas*. Bull. Acad. Natl. Med. Paris. 136:280-285.
- Willhite, C.Z. (1981) *Malformations induced by inhalation of acetonitrile vapors in the golden hamster*. Teratol. 23:69a.
- Willhite, C.Z. (1982) *Congenital malformations induced by laetrile*. Science 215:513.

Lead

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

Lead can be absorbed by the oral, inhalation or dermal exposure routes (see section on Relative Absorption Factors). Gastrointestinal absorption of lead varies considerably depending upon chemical form, dietary intake, and age (Forbes and Reina, 1974; Barltrop and Meek, 1975). The deposition and absorption of inhaled lead depends upon particle size, chemical form and the rate and depth of breathing (Randall et al., 1975; Nozaki, 1966; Chamberlain et al., 1975). Once absorbed, lead is distributed to the various organs of the body, with most distribution occurring into mineralized tissues (ATSDR, 1997). Placental transfer to the developing fetus is possible (Bellinger et al., 1987). Inorganic lead is not known to be biotransformed within the body. Absorbed lead is excreted via the urinary or fecal routes (ATSDR, 1997).

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

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

Results of *in vitro* studies with human lymphocyte cultures using lead acetate were nearly equally positive and negative. Results of *in vivo* tests are also contradictory but suggest that lead may have an effect on chromosomes (sister chromatid exchange). Results for gene mutations, DNA

modification, and recombinations in various microorganisms using lead acetate, lead nitrate and lead chloride were consistently negative with or without metabolic activation. Lead chloride has been reported to inhibit both DNA and RNA synthesis. In *in vitro* mammalian test systems, lead acetate gave conflicting results.

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

Agency for Toxic Substances and Disease Registry (ATSDR) (1997) Toxicological profile for lead. U.S. Public Health Service.

Barltrop, D. and Meek, F. (1975) *Absorption of different lead compounds*. Postgrad. Med. J. 51:805-809.

Bellinger, D.C., Leviton, A., Waternaux, C., Needleman, H. and Rabinowitz, M. (1987) *Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development*. N. Engl. J. Med. 316:1037-1043.

Benignus, V.A., Otto, D.A., Muller, K.E. and Seiple, K.J. (1981) *Effects of age and body lead burden on CNS function in young children. II: EEG spectra*. Electroencephalograph. Clin. Neurophysiol. 52:240-248.

Betts, P.R., Astley, R. and Raine, R.N. (1973) *Lead intoxication in children in Birmingham*. Br. Med. J. 1:402-406.

Boyland, E., Dukes, C.E., Grover, P.L. and Mitchley, B.C.V. (1962) *The induction of renal tumors by feeding lead acetate to rats*. Br. J. Cancer 16:283-288.

Chamberlain, D. et al. (1975) *Uptake of lead by inhalation of motor exhaust*. Proc. Roy. Soc. London B. 192:77-110.

Forbes, G.B. and Reina, J.C. (1974) *Effect of age on gastrointestinal absorption (Fe, Sr, Pb) in the rat*. J. Nutr. 102:647-652.

Fowler, B.A. et al. (1980) *Chronic low level lead toxicity in the rat: III. An integrated assessment of long-term toxicity with special reference to the kidney*. Toxicol. Appl. Pharmacol. 56:59-77.

Grant, L.D. et al. (1980) *Chronic low-level lead toxicity in the rat: II. Effects on postnatal physical and behavioral development*. Toxicol. Appl. Pharmacol. 56:42-58.

Hilderbrand, D.C. et al. (1973) *Effect of lead acetate on reproduction*. Am. J. Obstet. Gynecol. 115:1058-1065.

Ito, N. (1973) *Experimental studies on tumors on the urinary system of rats induced by chemical carcinogens*. Acta. Pathol. (Jap.) 23:87-109.

Kang, H.D. et al. (1980) *Occupational lead exposure and cancer: Letter to the Editor*. Science 207:935.

Kopp, L. et al. (1980a) *Altered metabolism and function of rat heart following chronic low level cadmium/lead feeding*. J. Mol. Cell. Cardiol. 12:1407-1425.

Kopp, L. et al. (1980b) *Cardiac physiological-metabolic changes after chronic low-level heavy metal feeding*. Am. J. Physiol. 239:H22-H30.

Nortier, J.W., Sangster, B. and Van Kestern, R.G. (1980) *Acute lead poisoning with hemolysis and liver toxicity after ingestion of red lead*. Vet. Hum. Toxicol. 22:145-147.

Nozaki, K. (1966) *Method for studies on inhaled particles in human respiratory system and retention of lead fume*. Ind. Health (Jap.) 4:118-128.

Randall, K. et al. (1975) *The effect of particle size on absorption of inhaled lead*. J. Am. Ind. Hyg. Assoc. 36:207-213.

Rom, W.N. (1976) *Effects of lead on female reproduction: A review*. Mt. Sinai J. Med. 43:542-552.

Schroeder, P. et al. (1970) *Zirconium, niobium, tin, vanadium, and lead in rats: Lifeterm studies*. J. Nutr. 100:59-68.

U.S. Environmental Protection Agency (USEPA) (1980) Ambient water quality criteria document for lead. Office of Regulations and Standards.

U.S. Environmental Protection Agency (USEPA) (1984) Drinking water criteria document on lead (Quantification of toxicological effects section) Office of Drinking Water.

Zawirska, B. and Medras, K. (1972) *The role of the kidneys in disorders of porphyrin metabolism during carcinogenesis induced with lead acetate*. Arch. Immunol. Ther. Exp. 20:257-272.

Manganese

Manganese is considered to be among the least toxic of the trace metals and, in fact, is considered to be an essential element (NRC, 1989). The oral absorption of dietary manganese ranges from 3 to 10% (ATSDR, 1997). However, manganese is absorbed to a greater extent

following inhalation exposures. The National Research Council has established a provisional recommended dietary allowance for adults of 2 to 5 mg/day (NRC, 1989). The effects following acute exposure to manganese are unknown. Chronic occupational exposure to manganese dust (0.02–2.6 mg/m³) has been associated with respiratory symptoms and pneumonitis (Chandra *et al.*, 1981) and higher levels have been associated with a condition known as manganism, a progressive neurological disease characterized by speech disturbances, tremors, and difficulties in walking. For example, male workers exposed to manganese dioxide, tetroxide and various salts (TWA of total airborne manganese dust ranged from 0.07 to 8.61 mg/m³) experienced an increased incidence of psychomotor disturbances (e.g., reaction time, hand-eye coordination and hand steadiness) (Roels *et al.*, 1987). Other effects observed in humans occupationally exposed to manganese dust include hematological (Chandra *et al.*, 1981; Flinn *et al.*, 1941; Kesic and Hausler, 1954), cardiovascular (Saric and Hrustic, 1975) and reproductive effects (Cook *et al.*, 1974; Emara *et al.*, 1971; Lauwerys *et al.*, 1985; Rodier, 1955). In adults, a safe intake of manganese from dietary sources ranges from 2 to 10 mg/day (10 mg/day = 0.14 mg/kg-day) (WHO, 1973; NRC, 1989; Schroeder *et al.*, 1966). Individuals who chronically ingested drinking water from natural wells containing manganese concentrations of 1,600–2,300 µg/L (0.06 mg/kg-day), showed a statistically significant increase in minor neurologic effects (neurologic exam scores) (Kondakis *et al.*, 1989). The dietary intake of manganese was unaccounted for in this study, and therefore, USEPA withdrew its previous assessment that used this study to determine a quantitative dose-response relationship for manganese in drinking water. Higher concentrations in drinking water (0.8 mg/kg-day) have resulted in symptoms including lethargy, increased muscle tonus, tremor and mental disturbances (Kawamura *et al.*, 1941). Chronic oral exposure of rats to manganese chloride can also result in CNS dysfunction (Leung *et al.*, 1981; Lai *et al.*, 1982). Chronic inhalation exposure of experimental animals (monkeys, rats, mice, hamsters) has resulted in respiratory effects; however, other studies have demonstrated that these effects may be immunological in origin (ATSDR, 1997). Manganese has not been reported to be teratogenic; however, this metal has been observed to cause depressed reproductive performance and reduced fertility in humans and experimental animals (USEPA, 1984a). Certain manganese compounds have been shown to be mutagenic in a variety of bacterial tests. Manganese chloride and potassium permanganate can cause chromosomal aberrations in mouse mammary carcinoma cells. Manganese was moderately effective in enhancing viral transformation of Syrian hamster embryo cells (USEPA, 1984a,b).

USEPA established a weight-of-evidence classification for manganese of D (not classifiable as to human carcinogenicity). USEPA derived an oral RfD of 1.4×10^{-1} mg/kg-day for total oral manganese ingestion based on a NOAEL of 0.14 mg/kg-day (10 mg/day) in humans chronically exposed to dietary levels (WHO, 1973; Schroeder *et al.*, 1966; NRC, 1989). The organ of concern was the CNS, and an uncertainty factor of one was used to derive the RfD. USEPA recommends a modifying factor of 3 to assess exposures from drinking water; therefore, an oral RfD of 2.4×10^{-2} mg/kg-day for drinking water has been derived.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for manganese*. U.S. Public Health Service.

Chandra, S.V., G.S. Shukla, R.S. Striavastava, H. Singh and V.P. Gupta. 1981. An exploratory study of manganese exposure to welders. *Clin. Toxicol.* 18:407-416.

- Cook, D.G., S. Fahn and K.A. Brait. 1974. Chronic manganese intoxication. *Arch. Neurol.* 30:59-64.
- Emara, A.M., S.H. El-Ghawabi, O.I. Madkour and G.H. El-Sarma. 1971. Chronic manganese poisoning in the dry battery industry. *Br. J. Ind. Med.* 28:78-82.
- Flinn, R.H., P.A. Neal and W.B. Fulton. 1941. Industrial manganese poisoning. *J. Ind. Hyg. Toxicol.* 23:374-387.
- Kawamura, R., H. Ikuta and S. Fukuzumi. 1941. Intoxication by manganese in well water. *Kitasato Arch. Exp. Med.* 18:145-149.
- Kesic, B. and V. Hausler. 1954. Hematological investigation on workers exposed to manganese dust. *Arch. Ind. Hyg. Occup. Med.* 10:336-343.
- Kondakis, X.G., M. Makris and M. Leotsinidis. 1989. Possible health effects of high manganese concentration in drinking water. *Arch. Environ. Health* 44:175-178.
- Lai, J.C.K., T.K.C. Leung and L. Lim. 1982. Activities of the mitochondrial NAD-linked isocitric dehydrogenase in different regions of the rat brain. Changes in aging and the effect of chronic manganese chloride administration. *Gerontology* 28:81-85
- Lauwerys, R., H. Roels and P. Genet. 1985. Fertility of male workers exposed to mercury vapor or to manganese dust: A questionnaire study. *Am. J. Ind. Med.* 7:171-176.
- Leung, T.K.C., J.C.K. Lai and L. Lim. 1981. The regional distribution of monoamine oxidase activities towards different substrates: Effects in rat brain of chronic administration of manganese chloride and of aging. *J. Neurochem.* 36:2037-2043.
- National Research Council (NRC). 1989. *Recommended dietary allowances*, 10th ed. Food and Nutrition Board, National Research Council. Washington, D.C.: National Academy Press. pp. 230-235.
- Rodier, J. 1955. Manganese poisoning in Moroccan miners. *Br. J. Ind. Med.* 12:21-35.
- Roels, H., R. Lauwerys and J-P. Buchet. 1987. Epidemiological survey among workers exposed to manganese: Effects on lung, central nervous system, and some biological indices. *Am. J. Ind. Med.* 11:307-327.
- Saric, M. and O. Hrustic. 1975. Exposure to airborne manganese and arterial blood pressure. *Environ. Res.* 10:314-318.
- Schroeder, H.A., D.D. Balassa and I.H. Tipton. 1966. Essential trace metals in man: Manganese, a study in homeostasis. *J. Chron. Dis.* 19:545-571.

U.S. Environmental Protection Agency (USEPA). 1984a. *Health assessment document for manganese. Final report*. Environmental Criteria and Assessment Office. EPA 600/8-83-013F. August 1984.

U.S. Environmental Protection Agency (USEPA). 1984b. *Health effects assessment for manganese (and compounds)*. Environmental Criteria and Assessment Office. EPA 540/1-86-057.

World Health Organization (WHO). 1973. *Trace elements in human nutrition: Manganese. Report of a WHO Expert Committee*. Technical Report Service, 532. Geneva, Switzerland: WHO. pp. 34-36.

Mercury

In humans, inorganic mercury is absorbed following inhalation and oral exposure; however, only 7-15% of administered inorganic mercury is absorbed following oral exposure (USEPA, 1984; Rahola *et al.*, 1971; Task Group on Metal Accumulation, 1973; ATSDR, 1997). Organic mercury is almost completely absorbed from the gastrointestinal tract and is assumed to be well absorbed via inhalation in humans (USEPA, 1984). A primary target organ for inorganic compounds is the kidney. Acute and chronic exposures of humans to inorganic mercury compounds have been associated with anuria, polyuria, proteinuria, and renal lesions (Goyer, 1996). Chronic occupational exposure of workers to elemental mercury vapors (0.026-0.2 mg/m³) has been associated with mental disturbances, tremors, and gingivitis (USEPA, 1984; ATSDR, 1993). Animals exposed to inorganic mercury for 12 weeks have exhibited proteinuria, nephrotic syndrome and renal disease (Druet *et al.*, 1978). Rats chronically administered inorganic mercury (as mercuric acetate) in their diet for 2 years exhibited a dose-related increase in glomerular nephritis at concentrations as low as 1.27 mg/kg-day (Fitzhugh *et al.*, 1950). The CNS is a major target for organic mercury compounds. Adverse effects in humans, resulting from subchronic and chronic oral exposures to organic mercury compounds, have included destruction of cortical cerebral neurons, damage to Purkinje cells, and lesions of the cerebellum. Clinical symptoms following exposure to organic mercury compounds have included paresthesia, loss of sensation in extremities, ataxia, and hearing and visual impairment (WHO, 1976; ATSDR, 1997). Adverse kidney effects are also prominent in animals following chronic ingestion of organic mercury (0.5 ppm phenyl mercuric acetate or 0.015 mg Hg/kg-day) (Fitzhugh *et al.*, 1950). Embryotoxic and teratogenic effects, including malformations of the skeletal and genitourinary systems, have been observed in animals exposed orally to organic mercury (USEPA, 1984). Both organic and inorganic compounds are reported to be genotoxic in eukaryotic systems (Leonard *et al.*, 1984). Elevated incidence of fetal resorption was observed in hamsters exposed to 31.4 mg/kg-day inorganic mercury (Gale, 1974). There is evidence to suggest methylmercury chloride induces renal tumors, mostly adenocarcinomas in two strains of male mice (ICR and B6C3F1) (Hirano *et al.*, 1986; Mitsumori *et al.*, 1981, 1990). However, monkeys, cats and rats chronically administered methyl mercury in the diet did not develop an elevated tumor incidence (Ikeda *et al.*, 1973; Charbonneau *et al.*, 1976; Vershuuren *et al.*, 1976). Furthermore, elevated cancer incidence has not been reported in humans who ingested methylmercury-contaminated fish in the Minamata area of Japan (Katsuna, 1968) or in humans who ingested methylmercury fungicide-treated grains in Iraq and were followed for 13 years (Greenwood, 1985).

USEPA reported an oral RfD for chronic exposures of 3×10^4 mg/kg-day for inorganic mercury based on the formation of mercury-induced autoimmune glomerulonephritis found in several oral and parenteral studies conducted in the Brown Norway rat studies (Druet *et al.*, 1978; Bernaudin *et al.*, 1981; Andres, 1984). An uncertainty factor of 1,000 was used to derive the RfD. An oral RfD of 1×10^4 mg/kg-day for methylmercury (organic) has been reported by USEPA based on several studies reporting human poisonings in particular fetal methylmercury poisoning in the relationship of maternal hair and child effects (Marsh *et al.*, 1987). An uncertainty factor of 10 was used to derive the RfD for methyl mercury.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for mercury*. U.S. Public Health Service.

Andres, P. 1984. Brief communication: IgA-IgG disease in the intestine of Brown-Norway rats ingesting mercuric chloride. *Clin. Immunol. Immunopathol.* 30:488-494.

Bernaudin, J.F., E. Druet, P. Druet and R. Masse. 1981. Inhalation or ingestion of organic or inorganic mercurials produces auto-immune disease in rats. *Clin. Immunol. Immunopathol.* 20: 488-494.

Charbonneau, S.M., I.C. Munro, E.A. Nera, F.A. Armstrong, R.F. Willes, F. Bryce and R.F. Nelson. 1976. Chronic toxicity of methylmercury in the adult cat. Interim report. *Toxicology* 5:337-349.

Druet, P., E. Druet, F. Potdevin and C. Sapin. 1978. Immune type glomerulonephritis induced by $HgCl_2$ in the brown Norway rat. *Ann. Immunol.* 129C:777-792.

Fitzhugh, O.G., A.A. Nelson, E.P. Laug and F.M. Kunze. 1950. Chronic oral toxicities of mercury-phenyl and mercuric salts. *Arch. Ind. Hyg. Occup. Med.* 2:433-441.

Gale, T.F. 1974. Embryopathic effects of different routes of administration of mercuric acetate on the hamster. *Environ. Res.* 8:207-213.

Greenwood, M.R. 1985. Methylmercury poisoning in Iraq. An epidemiological study of the 1971-1972 outbreak. *J. Appl. Toxicol.* 5:148-159.

Goyer, R.A. 1996. Toxic Effects of Metals. In: *Casarett and Doull's toxicology: The basic science of poisons*, ed. C.D. Klaassen, 5th ed. New York: McGraw-Hill. pps. 709-718.

Hirano, M., K. Mitsumori, K. Maita and Y. Shirasu. 1986. Further carcinogenicity study of methylmercury chloride in ICR mice. *Jpn. J. Vet. Sci.* 48:127-135.

Ikeda, Y., M. Tobe, K. Kobayashi, S. Suzuki, Y. Kawasaki and H. Yonemaru. 1973. Long-term toxicity study of methylmercuric chloride in monkeys. *Toxicology* 1:361-375.

- Katsuna, M. 1968. *Minamata disease. Study group of Minamata disease.* Kumamota University, Japan.
- Leonard, A., G.B. Gerber, P. Jacquet and R.R. Lauwerys. 1984. Mutagenicity, carcinogenicity, and teratogenicity of industrially used metals. In: *Mutagenicity, carcinogenicity and teratogenicity of industrial pollutants*, ed. M. Kirsch-Volders. New York: Plenum Press. pp. 59-126.
- Marsh, D.O., T.W. Clarkson and C. Cox. 1987. Fetal methylmercury poisoning: relationship between concentration in single strands of maternal hair and child effects. *Arch. Neurol.* 44:1017-1022.
- Mitsumori, K., K. Maita, T. Saito, S. Tsuda and Y. Shirasu. 1981. Carcinogenicity of methylmercury chloride in ICR mice: Preliminary note on renal carcinogenesis. *Cancer Lett.* 12:305-310.
- Mitsumori, K., M. Hirano, H. Ueda, K. Maita and Y. Shirasu. 1990. Chronic toxicity and carcinogenicity of methylmercury chloride in B6C3F1 mice. *Fundam. Appl. Toxicol.* 14:179-190.
- Rahola, T., T. Hattula, A. Korlainen and J.K. Miettinen. 1971. The biological halftime of inorganic mercury (Hg^{2+}) in man. *Scand. J. Clin. Invest.* 27(suppl. 116):77.
- Task Group on Metal Accumulation. 1973. Accumulation of toxic metals with special reference to their absorption, excretion and biological halftimes. *Environ. Phys. Biochem.* 3:65-67.
- U.S. Environmental Protection Agency (USEPA). 1984. Health effects assessment for mercury. Environmental Criteria and Assessment Office. EPA 540/1-86-042.
- Vershuuren, H.G., R. Kroes, E.M. Den Tonkelaar, P.L. Schuller and G.J. Van Esch. 1976. Toxicity of methylmercury chloride in rats. III. Long-term toxicity study. *Toxicology* 6:107-123.
- World Health Organization (WHO). 1976. *Environmental health criteria, mercury.* Geneva, Switzerland: WHO.

Thallium

Thallium and its salts are readily and rapidly absorbed through the skin, lungs, and mucous membranes of the mouth and gastrointestinal tract (ATSDR, 1997). Percutaneous absorption has also been reported to occur through rubber gloves (Rumack, 1986). Thallium is acutely toxic to humans regardless of the chemical form of the compound or route of administration. Hundreds of cases of thallosis due to ingestion of thallium-based pesticides have been reported (ACGIH, 1986). Children poisoned by thallium ingestion have exhibited neurological abnormalities including mental retardation and psychoses (ACGIH, 1986). The effects of thallium toxicity are similar in humans and animals. The most commonly noted response to

thallium exposure is alopecia, but neurological and gastrointestinal findings are frequently found. Such effects include ataxia, lethargy, painful extremities, peripheral neuropathies, convulsions, endocrine disorders, psychoses, nausea, vomiting, and abdominal pains (Bank, 1980). It has been noted that the degree and duration of exposure to thallium and its salts can influence the clinical picture of thallium intoxication. Subchronic feeding studies conducted with rats observed marked growth depression and a nearly complete loss of hair (USEPA, 1986; Clayton and Clayton, 1981). Exposure to thallium salts during critical developmental stages in chicks and rats has been reported to be associated with the induction of adverse developmental outcomes (Karnofsky *et al.*, 1950). Pre- and postnatally exposed rat pups have exhibited hydronephrosis, fetal weight reduction and growth retardation (Clayton and Clayton, 1981; Gibson and Becker, 1970). Thallium has also been shown to cross the placenta and, presumably, enter the fetal blood system (Clayton and Clayton, 1981). Thallium has not been demonstrated to be carcinogenic in humans or experimental animals and may have some antitumor activity (Clayton and Clayton, 1981).

USEPA derived oral RfDs for certain thallium salts (i.e., thallium acetate, thallium carbonate, thallium chloride, thallium nitrate, thallium selenite and thallium sulfate) of between $8-9 \times 10^{-5}$ mg/kg-day based on the same 90-day subchronic rat study (USEPA, 1986; MRI, 1986). For this risk assessment, an oral RfD of 8×10^{-5} mg/kg-day for thallium salts is used to assess all thallium exposures. The same endpoints of toxicity were observed and an uncertainty factor of 3,000 was used to derive the chronic RfD.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for thallium*. U.S. Public Health Service.

American Conference of Governmental Industrial Hygienists (ACGIH). 1986. *Documentation of the threshold limit values and biological exposure indices*. Cincinnati: ACGIH.

Bank, W.J. 1980. Thallium. In: *Experimental and clinical neurotoxicology*, eds. P.S. Spencer and H.H. Schaumberg. Baltimore, MD: Williams and Wilkins. p. 571.

Clayton, G.D. and F.E. Clayton. 1981. *Patty's industrial hygiene and toxicology*. 3rd ed. New York: John Wiley and Sons. p. 1916.

Gibson, J.E. and B.A. Becker. 1970. Placental transfer, embryo toxicity, and teratogenicity of thallium sulfate in normal and potassium-deficient rats. *Toxicol. Appl. Pharmacol.* 16:120-132.

Karnofsky, D.A., L.P. Ridgway and P.A. Patterson. 1950. Production of achondroplasia in the chick embryo with thallium. *Proc. Soc. Exp. Biol. Med.* 73:255-259.

Midwest Research Institute (MRI). 1986. Subchronic (90-day) toxicity study of thallium sulfate in Sprague-Dawley rats. Office of Solid Waste.

Rumack, B.H. 1986. *Poisindex*. Microfiche ed. Micromedix, Inc., Denver, Colorado, in association with the National Center for Poison Information, with updates, 1975-present.

U.S. Environmental Protection Agency (USEPA). 1986. *Subchronic (90-day) toxicity of thallium (I) sulfate in Sprague-Dawley rats. Final report.* Office of Solid Waste. Project No. 8702-1(18).

Vanadium

The absorption of vanadium through the gastrointestinal tract of animals is low (2.6% for vanadium pentoxide in rats) (Conklin *et al.*, 1982). Soluble vanadium compounds that are inhaled and deposited are readily absorbed (50–100%) (ATSDR, 1997). Because vanadium has low solubility, its absorption through skin is thought to be quite low, although no specific studies were located regarding dermal absorption (ATSDR, 1997). Pentavalent vanadium compounds are generally considered to be more toxic than other valence states. Many incidents of short-term and long-term occupational exposures to vanadium, mainly vanadium pentoxide dust, have been reported. Inhalation causes respiratory tract irritation, coughing, wheezing, labored breathing, bronchitis, chest pains, eye and skin irritation and discoloration of the tongue (NIOSH, 1977; NAS, 1974). Humans subchronically exposed to vanadium pentoxide (0.1 mg/m³) via inhalation experienced respiratory irritation (Zenz and Berg, 1967). Experimental animals (i.e., rats, monkeys) subchronically exposed to vanadium compounds (vanadium pentoxide, bismuth orthovanadate) manifested alveolar proteinosis and increased pulmonary resistance at concentrations of 2.5–4.7 mg/m³ (Lee and Gillies, 1986; Knecht *et al.*, 1985). Effects seen in experimental animals following chronic inhalation exposure include fatty degeneration of the liver and kidneys, hemorrhage, and bone marrow changes (Browning, 1969). Humans subchronically exposed to ammonium vanadyl tartrate (1.3 mg/kg-day) via capsules did not manifest any adverse effects (Dimond *et al.*, 1963). However, experimental animals (i.e., rats, mice) orally exposed to vanadium compounds (sodium metavanadate, sodium orthovanadate, ammonium metavanadate) exhibited mild systemic effects (decreased weight gain, vascular infiltration, spleen hypertrophy and increased ventricular pressure) at doses as low as 0.57 mg/kg-day (ATSDR, 1997). Rats chronically administered 0.77 mg/kg-day (5 ppm) vanadium in their drinking water showed no adverse effects (Schroeder *et al.*, 1970). Pre- and postnatally exposed rat pups have exhibited reduced pup weight and length and facial hemorrhage (ATSDR, 1997). Vanadium has not been demonstrated to be carcinogenic in humans or experimental animals.

USEPA reports a chronic oral RfD of 7×10^{-3} mg/kg-day based on a chronic study in which rats received vanadium in their drinking water (Schroeder *et al.*, 1970). A NOAEL of 0.77 mg/kg-day (5 ppm) and an uncertainty factor of 100 were used to develop the RfD.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological profile for vanadium.* U.S. Public Health Service.

Browning, E. 1969. *Toxicity of industrial metals.* 2nd ed. New York: Appleton-Century-Crofts.

Conklin, A.W., C.S. Skinner and T.L. Felten. 1982. Clearance and distribution of intratracheally instilled vanadium — 48 compounds in the rat. *Toxicol. Lett.* 11:199-203.