ATTACHMENT 4. TOXICOLOGICAL PROFILES FOR CHEMICALS OF POTENTIAL CONCERN

Attachment 4. Toxicological Profiles for Chemicals of Potential Concern

The following sections provide toxicological information for each of the chemicals that were identified as COPCs in this human health risk assessment (HHRA). The toxicity values used in this risk assessment (i.e., RfD or SF) are in bold type. Toxicity information was obtained primarily from:

- US Environmental Protection Agency (EPA's) Integrated Risk Information System (IRIS) (EPA 2006b)
- EPA's 1997 Health Effects Summary Tables (HEAST)(EPA 1997b)
- Toxicological profiles presented in *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories* (EPA 2000)
- EPA's Office of Ground Water and Drinking Water (OGWDW) (EPA 2006a)
- Agency for Toxic Substance and Disease Registry (ATSDR; 2006b)
- ToxFAQs (ATSDR 2006a)
- Hazardous Substance Data Bank (HSDB) (TOXNET 2006)

Since quantitative estimates of toxicity potential have been developed by EPA and other agencies, it is necessary to establish a hierarchy to determine what toxicity values should be used. EPA (2003b) has developed a hierarchical order of toxicity values for use in human health risk assessments:

- Tier 1 – EPA's IRIS
- Tier 2 – EPA's Provisional Peer Reviewed Toxicity Values (PPRTVs), Office of Research and Development/National Center for Environmental Assessment
- Tier 3 – Other toxicity values. Tier 3 includes additional EPA and non-EPA sources of toxicity information. Priority is given to those sources of information that are the most current, the basis for which is transparent and publicly available, and which have been peer reviewed. Sources include EPA Regional offices, EPA HEAST values, Cal/EPA, and ATSDR minimal risk levels (MRLs).

Online versions of IRIS, HSDB, and ToxFAQs are cited by acronym only in the sections below. These databases were accessed between February and April 2006. Other citations are presented in standard form. The carcinogenic evaluation of chemicals by the International Agency for Research on Cancer (IARC) and toxicity evaluations by the National Center for Environmental Assessment (NCEA, a division of EPA), as cited in other documents, are also referred to by their acronyms.

Glossary

Anorexia	An abnormal loss of appetite and desire to eat that results in severe weight loss.
Aplastic anemia	A condition whereby the capacity of bone marrow to generate red blood cells is defective.
Ataxia	The sudden onset of uncoordinated muscle movement.
Bronchiolitis	Inflammation of the small airways of the lung.
Chloracne	A rare acne-like skin condition caused by certain toxic chemicals.
Cirrhosis	A chronic disease of the liver that results in scarring of the liver and liver dysfunction.
Coma	A state of unconsciousness in which a person is unable to respond to stimuli.
Contact dermatitis	An inflammation of the skin caused by direct contact with an irritating or allergy-causing substance.
Conjunctivitis	An inflammation of the clear membrane that covers the white part of the eye and lines the inner surface of the eyelids, commonly known as pinkeye.
Cyanosis	A bluish discoloration of the skin or mucous membranes caused by lack of oxygen in the blood.
Defoliant	Any substance designed to destroy or remove foliage.
Dyspnea	Difficulty breathing or shortness of breath.
Edema	Swelling or enlargement of organs, skin, or other parts of the body caused by the excessive buildup of fluid in tissue.
Erythrocyte	Red blood cell.
Fungicide	Any substance used to kill fungus.
Gout	A disorder in which the body overproduces or cannot eliminate uric acid, which results in joint pain, especially in the feet and legs.

Hemoglobin	The red substance in blood that carries oxygen to cells throughout the body.
Hemolysis	The premature breakdown and destruction of red blood cells, which results in an inadequate number of red blood cells for the transport of oxygen.
Hemolytic anemia	A condition in which an inadequate number of circulating red blood cells (anemia) is caused by the premature destruction of red blood cells.
Herbicide	Any substance used to kill plants.
Jaundice	A condition, characterized by a yellow color in the skin, the mucous membranes, or the eyes, in which bilirubin, a byproduct of old red blood cells, is not adequately eliminated from the body.
Keratitis	Also known as dry-eye syndrome, a condition in which tear glands produce fewer tears.
Lacrimation	The production of tears; crying.
Lethargy	A feeling of fatigue, tiredness, or general lack of energy.
Leukocyte	White blood cell.
Leukemia	A type of cancer that targets bone marrow and causes an uncontrolled increase in the production of white blood cells.
LOAEL	Lowest-observed-adverse-effect level. The lowest dose at which an adverse reaction to a chemical or substance was observed.
LD50	Lethal dose at 50%. The amount of a chemical or other toxic substance that is sufficient to kill 50% of a population of test animals.
Lymphocyte	The nearly colorless cells formed in lymphatic tissue (lymph nodes, spleen, thymus, and tonsils) that constitute nearly a third of all white blood cells in the blood.
Lymphoma	Malignancy (cancer) of lymph tissue found in the lymph nodes, spleen, liver, and bone marrow.

Malaise	A general, non-specific feeling of discomfort, illness, or lack of well-being, often accompanied by exhaustion or low energy.
Methemoglobin anemia	See Methemoglobinemia.
Methemoglobinemia	A condition in which the iron in red blood cells is defective, which prevents it from transporting oxygen effectively.
Methemoglobinuria	The presence of methemoglobin in urine.
Necrosis	Death of cells or tissue caused by injury or disease, especially in a localized area of the body.
Necrotizing bronchitis	Bronchitis characterized by cell death in the airways or deeper tissues of the lungs.
NOAEL	No-observed-adverse-effect level. The highest dose at which no effect was observed from exposure to a certain chemical or toxic agent.
Pesticide	Any substance used to repel or kill pests.
Pulmonary edema	Fluid accumulation and swelling in the lungs.
Pulmonary fibrosis	The scarring or thickening of tissues deep in the lung without a known cause.
Proteinuria	The presence of protein in urine.
Rhinitis	A condition characterized by a constant runny nose, sneezing, and nasal congestion.
Siderosis	Chronic inflammation of the lungs caused by excessive inhalation of dust that contains iron. May also refer to the discoloration of organs or tissue as the result of excess iron in the blood.
Tachycardia	Irregular heartbeat or palpitations, often accompanied by sensations of heart pounding or racing.
Vertigo	A sudden sensation of spinning or dizziness, typically provoked by head movement.

Toxicological Profiles for Principal Risk Drivers

1. 2,3,7,8-TCDD (DIOXIN)

Tetrachlorodibenzo-*p*-dioxin (TCDD) is produced as an unwanted contaminant during the manufacture of chlorobenzenes, chlorophenols and their derivatives. TCDD is the most toxic of the 210 polychlorinated dioxin and furan congeners, although it should be noted that other congeners are also quite toxic. TCDD is released to the environment primarily through emissions from the incineration of municipal and chemical wastes, in exhaust from automobiles using leaded gasoline, and from the improper disposal of certain chlorinated chemical wastes. The major route of exposure to dioxins for the general population is through the ingestion of food, a result of the highly bioaccumulative nature of dioxins (Schecter and Gasiewicz 2001). Exposure can also occur through the inhalation of output from various incineration processes and exhausts from leaded gasoline engines. However, the main issue with these emissions is that they accumulate in virtually all food products, where they are ingested by humans (HSDB).

Pharmacokinetics

Dioxins are absorbed through the gastrointestinal tract, respiratory tract, and skin and distributed throughout the body. Absorption is congener-specific, with decreased absorption of hepta- and octa-congeners compared with dioxins with fewer chlorines. Because of their lipophilic nature, dioxins tend to accumulate in fat and the liver. Dioxins are slowly metabolized by oxidation or reductive dechlorination and conjugation, and the major routes of excretion are the bile and feces. Reported half lives in the body range from 5 to 15 years. Small amounts may be eliminated in the urine (EPA 2000).

Acute toxicity

The most commonly reported symptom related to TCDD exposure in humans is chloracne. The lesions of the skin may develop a few weeks after the exposure and may persist for over a year following the cessation of exposure. Other skin problems which have been reported include hyperpigmentation, hirsutism, increased skin fragility, and vesicular eruptions on exposed areas of the skin. Other less consistently reported non-carcinogenic effects from dioxin exposure in humans include asthenia, headaches, and pain in the extremities, peripheral neuropathy, ulcers, altered liver function, enzyme induction, altered lipid metabolism, and abnormal urinary porphyrin patterns. Immune system dysfunction and altered T-cell subsets have been reported by some investigators but have not been found by others (HSDB).

Chronic toxicity

In animal studies, numerous effects have been documented, including hepatic, gastrointestinal, hematological, dermal, body weight changes, endocrine, immunological, neurological, reproductive, and developmental effects. Most of the studies have involved oral exposure.

In humans, even low levels of dioxin exposure have been shown to have adverse health effects (EPA 2003a). The effect most commonly associated with exposure to dioxin-like agents is the skin disease chloracne, a particularly severe and prolonged acne-like skin disorder. Human studies have also shown that numerous developmental effects occurred after dioxin exposure (Mocarelli et al. 1991). Adverse human health effects were also noted following consumption of heated rice oil contaminated with PCBs and chlorinated dibenzofurans (CDFs). Some epidemiological studies have suggested that dioxins may cause immunosuppression, respiratory effects, cardiovascular effects, and liver effects in humans (EPA 2000). EPA has not developed an RfD for dioxins because the United States population is already exposed to unsafe levels of dioxins as a result of background concentrations of this chemical in most food items (EPA 2003a).

Carcinogenicity

There is limited evidence in humans for the carcinogenicity of TCDD, although there is sufficient evidence in experimental animals for the carcinogenicity of TCDD. The World Health Organization (IARC 1995) has concluded that TCDD is carcinogenic to humans (Group 1). In making the overall evaluation, the Working Group took into consideration the following supporting evidence: 1) TCDD is a multi-site carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor, 2) this receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental animals, and 3) tissue concentrations are similar in both heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays.

To assess the risk associated with dioxins, it is important to understand that although 2,3,7,8-TCDD is the most toxic congener, many other congeners are also quite toxic and are important because of the additive nature of dioxin toxicity. For this reason, a toxic equivalency (TEQ) approach is used for dioxin and dibenzofuran congeners, where the toxic equivalency factor (TEF) for each congener is applied to determine the overall dioxin toxicity. The TEQ approach is discussed in greater detail in Sections B.2.2 and B.4 of the risk assessment. EPA has established 2,3,7,8-TCDD as a probable human carcinogen (category B2) and has established an **oral cancer slope factor of 150,000 per mg/kg-day** (IRIS). Since 2,3,7,8-TCDD is the most toxic congener, the cancer slope factor for this chemical is used to ensure a conservative estimate of dioxin toxicity.

2. ARSENIC

Arsenic is a naturally occurring element in the earth's crust that is usually found combined with other elements. Arsenic combined with elements such as oxygen, chlorine, and sulfur is referred to as inorganic arsenic; arsenic combined with carbon and hydrogen is referred to as organic arsenic. Arsenic in seafood is more commonly in the organic form (EPA 1997a). Most of the common organic forms, such as arsenobetaine and arsenocholine, are non-toxic, but other forms that may also occur to some extent, such as dimethylated and monomethylated arsenic acids, are more toxic (EPA 1997a). Some seafood may also contain arseno-sugars, which may be metabolized to dimethyl arsenic (Chew 1996).

Pharmacokinetics

Pharmacokinetic studies show that water-soluble arsenic compounds are well absorbed across the gastrointestinal tract. They appear to be transported throughout the body; analysis of tissues taken at autopsy from people who were exposed to arsenic found arsenic present in all tissues of the body. The arsenic levels in hair and nails were the highest, with somewhat lower levels in internal organs (ATSDR 2005a).

The metabolism of arsenic consists mainly of a reduction reaction, which converts pentavalent arsenic to trivalent arsenic, and methylation reactions, which convert arsenite to monomethylarsonic acid and dimethylarsenic acid (EPA 2000). Recent research suggests that trivalent forms of methylated arsenic generated during methylation may be more toxic than inorganic arsenic (Petrick et al. 2000; Petrick et al. 2001; Thomas et al. 2001). The primary excretion route for arsenic and metabolites is in the urine, with human studies showing that 45 to 85 percent is excreted in the urine within 1 to 3 days. Very little is excreted in the feces (ATSDR 2005a).

Acute toxicity

Arsenicals have been recognized as a human poison since ancient times, and large doses, approximately 600 µg/kg-day or higher, taken orally have resulted in death (EPA 2000). Oral exposure to lower levels of arsenic has resulted in effects on the gastrointestinal system (nausea, vomiting); central nervous system (headaches, weakness, delirium); cardiovascular system (hypotension, shock); and the liver, kidney, and blood (anemia, leucopoenia). Because significant information is available on the acute effects of arsenic poisoning in humans, few animal studies have been carried out. The limited available data have shown arsenic to have low to moderate acute toxicity to animals, based on LD50s between 50 and 5,000 mg/kg (ATSDR 2005a).

Chronic toxicity

The primary effects noted in humans from chronic exposure to arsenic are effects on the skin. Oral exposure has resulted in a pattern of skin changes that include the formations of warts or corns on the palms and soles, along with areas of darkened skin

on the face, neck, and back (EPA 2000). Blackfoot disease, a disease characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene, is associated with arsenic (ATSDR 2005a). Other effects noted from chronic oral exposure include peripheral neuropathy, cardiovascular disorders, and liver and kidney disorders.

EPA's IRIS database provides an **RfD for inorganic arsenic of 0.0003 mg/kg-day**, based on a no observed adverse effects level (NOAEL) (adjusted to include arsenic exposure from food) of 0.0008 mg/kg-day. The RfD was based on two studies that showed that the prevalence of blackfoot disease increased with both age and dose for individuals exposed to high levels of arsenic in drinking water.

Carcinogenicity

There is clear evidence that chronic exposure of humans to inorganic arsenic increases the risk of cancer. Ingestion of arsenic has been associated with an increased risk of non-melanoma skin cancer, and bladder, liver, and lung cancer. In addition, studies have reported that inhalation of arsenic results in an increased risk of lung cancer (EPA 2000). Dimethyl arsenic may be a promoter of various forms of cancer in rats and mice (Kenyon and Hughes 2001). EPA has classified inorganic arsenic in Group A—Known Human Carcinogen, based on the increased incidence in humans of lung cancer through inhalation exposure and the increased risk of skin, bladder, liver, and lung cancer through drinking water exposure.

The **oral cancer slope factor for arsenic is 1.5 per mg/kg-day** (IRIS). EPA used data from Taiwan concerning skin cancer incidence, age, and level of exposure via drinking water. In 37 villages that had obtained drinking water for 45 years from artesian wells with various elevated levels of arsenic, 40,421 individuals were examined for hyperpigmentation, keratosis, skin cancer, and blackfoot disease. The local well waters were analyzed for arsenic, and the age-specific cancer prevalence rates were correlated with both local arsenic concentrations and duration of exposure.

3. CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS (cPAHs)

PAHs are a group of organic chemicals that have a fused ring structure of two or more benzene rings, and are formed during the incomplete combustion of organic materials. Industrial activities which produce PAHs include: coal coking, production of carbon blacks, creosote, coal tar, petroleum refining, synfuel production from coal, and the use of Soderberg electrodes in aluminum smelters and ferrosilicum and iron works (EPA 2000). Domestic activities which produce PAHs include: cigarette smoke, burning of wood and fossil fuels, waste incineration, broiling and smoking foods, and the use of combustion engines. Benzo(a)pyrene is the PAH with the most available health effects data.

Pharmacokinetics

PAHs can be absorbed through the lungs, the stomach, or the skin. Oral absorption increases with more lipophilic PAHs or in the presence of oil in the gastrointestinal tract. Upon inhalation, oral or dermal exposure of animals, the highest levels of PAHs were found in highly perfused tissues, such as the lung, liver, gastrointestinal tract and kidneys. It has been demonstrated that PAHs metabolize to reactive intermediates by enzyme systems, which then covalently bind to cellular macromolecules leading to mutation and tumor development (EPA 2000).

Acute toxicity

There are little data describing acute toxicity of PAHs after inhalation, oral, or dermal exposure in humans or animals. However, benzo(a)pyrene is fatal to mice following ingestion, and the liver and the skin have been identified as target organs in animals after oral or dermal exposure, respectively (ATSDR 1995). The intraperitoneal LD50 values (injected dose which kills ½ of the animals being tested) in mice for pyrene, anthracene, and benzo(a)pyrene are 514, >430, and 232 mg/kg, respectively.

Chronic toxicity

PAHs have a high chronic exposure toxicity characterized by chronic dermatitis and hyperkeratosis (ATSDR 1995). Chronic studies in animals exposed to PAHs via ingestion, intratracheal installation, or skin-painting have not as yet identified adverse health effects other than cancer. RfDs have not been developed for any of the carcinogenic PAHs being evaluated in this Phase 1 HHRA.

Carcinogenicity

Occupational studies of workers exposed to mixtures containing PAHs have shown that mixtures of PAHs are carcinogenic to humans. Cancer associated with exposure to PAH containing mixtures in humans occurs mainly in the lung and skin following inhalation and dermal exposure.

The EPA and California EPA describe the cancer causing ability of individual cPAHs relative to the cancer causing ability of a reference compound, benzo(a)pyrene (EPA 1993; California EPA 1994). This approach is described in greater detail in Sections B.2.2 and B.4 of the risk assessment. The oral cancer slope factor developed by EPA for carcinogenicity of benzo(a)pyrene is **7.3 per mg/kg-day** (IRIS). EPA has classified benzo(a)pyrene as a probable human carcinogen (B2) based on observations of significant dose-related increases in multiple studies of rats and mice of both sexes (IRIS). The oral cancer potency factor was applied to the sum of cPAHs, using the TEFs described in Section B.2.2.

4. POLYCHLORINATED BIPHENYLS (PCBS)

Although the production and use of PCBs were banned in this country in 1979, this chemical group is extremely persistent in the environment and bioaccumulates

through the food chain (EPA 2000). There is evidence that some dioxin-like PCB congeners, which are assumed to be the most toxic, preferentially accumulate in organisms higher on the food chain, including humans. As a result, the composition of PCB mixtures in fish tissue may differ significantly from the environmental PCB source. Often the mixtures of interest are not those that have been used in studies of laboratory animals to determine toxicity (EPA 2000).

Pharmacokinetics

PCBs are absorbed through the gastrointestinal tract and distributed throughout the body, although the highest accumulation is typically in lipid-rich tissues. Human milk may contain relatively elevated PCB concentrations due to its high fat content (ATSDR 2000b).

The retention of PCBs in fatty tissues is linked to the degree of chlorination and also to the position of the chlorine atoms in the biphenyl ring. In general, more chlorinated congeners persist for longer periods of time. In occupationally exposed individuals, less chlorinated congeners had half-lives between 1 and 6 years, while more chlorinated congeners had half-lives ranging from 8 to 24 years (ATSDR 2000b). In subjects who consumed PCB-contaminated rice in Taiwan, the half-lives of several PCBs ranged from 3 to 24 months (EPA 2000).

Acute toxicity

Studies in animals have shown that exposure to very high doses of PCBs can cause death. However, doses of such magnitude are unlikely in environmental exposures and current industrial settings. There have been no reports of deaths in humans after exposure to PCBs even where exposures were much higher than those typically identified with environmental exposures (ATSDR 2000b).

Chronic toxicity

Numerous effects have been documented in animal studies including hepatic, gastrointestinal, hematological, dermal, body weight, endocrine, immunological, neurological, reproductive, developmental, and liver cancer (ATSDR 2000b). One of the most distinct effects associated with PCB exposure is the skin condition chloracne, which is generally associated with high levels of exposure (ATSDR 2000b). Evidence of other chronic effects in humans is not nearly as definitive. Several studies in humans have suggested that PCB exposure, particularly via in utero exposure through maternal fish consumption, may cause adverse effects in children and in developing fetuses (ATSDR 2000b). Neurobehavioral effects in such children with a range of PCB exposure levels have been documented by Fein et al. (1984), Jacobson and Jacobson (1996; 1997), and Schantz (1996). A review of exposure evaluation in 10 more recent studies associating neurodevelopmental effects with PCBs is also available (Longnecker et al. 2003). This will facilitate future comparisons across studies and future updates to neurodevelopmental toxicity metrics. PCBs have also been

associated with immunological effects in several epidemiological studies (Dallaire et al. 2006).

Over intermediate durations (i.e., less than 10% of an organism's lifetime), learning problems have been noted in monkeys fed PCB mixtures similar in composition to human breast milk (ATSDR 2000b). Some studies also indicate a possible connection between PCB exposure and cardiovascular effects; although this has been better demonstrated in assessments of dioxins, which share a similar chemical structure to PCBs (see structure activity relationships at the end of the PCB section).

EPA has derived an **RfD of 0.00002 mg/kg-day** for Aroclor 1254 (IRIS). The RfD was based on a LOAEL of 0.005 mg/kg-day for ocular and immunological effects in monkeys. This RfD is considered to be protective of developmental effects as well, and is used for total PCBs in this HHRA.

Carcinogenicity

PCBs are classified by EPA as Class B2, probable human carcinogens. This designation is based on studies that have found liver tumors in rats exposed to Aroclors 1260, 1254, 1242, and 1016. Occupational mortality data indicate that exposures to PCBs during capacitor manufacturing and repairing were associated with cancer of the liver, biliary tract and/or gall bladder, intestinal cancer, and skin melanoma (Brown and Jones 1981; Brown 1987); however, previous reviews of human epidemiological studies of PCBs have not yielded conclusive results (Silberhorn et al. 1990). Some more recent studies have indicated an increase in melanoma, brain, prostate, or liver cancer mortality in populations occupationally exposed to PCBs (Prince et al. 2006a; Prince et al. 2006b; Ruder et al. 2006). Elevated risk of non-Hodgkin lymphoma has been associated with detection of PCBs in carpet dust (Colt et al. 2005) and in elevated PCB concentrations in blood (De Roos et al. 2005).

EPA has developed a range of slope factors for PCBs (EPA 1996). Using information on environmental processes, they have provided guidance for choosing an appropriate slope factor based on the class of the mixture and the exposure pathway. Because bioaccumulated PCBs appear to be more toxic and more persistent in the body than commercial PCBs, **the upper bound slope factor associated with high risk and persistence (2.0 per mg/kg-day) was used in this HHRA** (IRIS).

When assessing PCB mixtures, it is important to recognize that both dioxin-like and non-dioxin-like modes of action contribute to overall PCB toxicity. It is possible that concentrations of dioxin-like congeners are increased in an environmental mixture. When congener concentrations are available, the mixture-based approach based on Aroclor analyses can be supplemented by analysis of dioxin TEQs to evaluate the PCB congeners with dioxin-like toxicity. In the TEQ approach, all PCB congeners with dioxin-like properties are analyzed in order to assess their impact on the overall risk from PCBs. For the analysis of dioxin-like PCB congeners, the **dioxin slope factor of 150,000 per mg/kg-day** (EPA 2005) is used with the estimated dioxin toxic equivalency

(Van den Berg et al. 2006). Details of the structure activity relationship are presented below. The TEFs for PCBs are presented in Section B.2.2.

Structure Activity Relationships

Some non- and mono-ortho substituted PCBs may adapt a planar conformation and activate the aryl hydrocarbon (Ah) receptor. These PCBs are thought to share a common mode of toxic action with dioxin (2,3,7,8-TCDD) and are sometimes referred to as dioxin-like PCBs (Van den Berg et al. 2006). Some polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are also capable of activating the Ah receptor and also have TEFs (see Section B.2.2). The mono-ortho substituted PCBs have higher TEFs because they are structurally better able to take on the planar conformation needed to activate the Ah receptor.

A recent study assessed cancer in rodents exposed to an equal TEQ quantity from either one PCB, one PCDF, a mixture (equal parts of one PCB, one PCDF, and TCDD), or TCDD (Walker et al. 2005). The results of this study supported the use of the TEF approach for the estimation of PCB cancer risk.

PCBs used in most laboratory studies and found in the environment are complex mixtures, and it is not known exactly what portion of observed effects is attributable to dioxin-like or non-dioxin-like PCBs. The EPA Science Advisory Board cited the van der Plas et al. (2000) study of rats exposed to Aroclor 1260, which suggested that most of the tumor promotion potential of PCB mixtures is attributable to the non-dioxin-like fraction (EPA 2001). Because this fraction is not included in the TEQ calculation, van der Plas et al. (2000) concluded that the tumor promotion potential of PCBs might be underestimated by the TEQ approach alone. This is also supported by estimates of TEQs for the different Aroclors. Although EPA's SF included consideration of several Aroclors, the SFs for 1260, followed by 1254, were the highest in the studies evaluated and were used for the development of the SF for total PCBs (EPA 1996). The TEQ potency for Aroclor 1260 on a mass basis is lower than the potencies for several other Aroclors (Rushneck et al. 2004; Van den Berg et al. 2006). This also suggests that some of its carcinogenic potency is not attributable to dioxin-like PCB congeners.

Another recent review also supports PCB carcinogenicity as acting through an indirect mechanism, such as tumor promotion (rather than initiation) (Knerr and Schrenk 2006). Across the carcinogenicity studies evaluated, the TEQ dose (but not the total PCB dose) was found to be primarily responsible for the development of neoplasms in rats. However, tumor promotion experiments in rodents have shown that both dioxin-like and non-dioxin-like PCB congeners may act as liver tumor promoters. In the case of the van der Plas (2000) study, Knerr and Schrenk (2006) asserted that the purity data provided in that study were not sufficient to exclude the potential contribution of some dioxin-like PCB congeners to the observed toxicity (Knerr and Schrenk 2006). Although the dioxin-like PCB congeners showed much greater potency, some weak carcinogenic potency of non-dioxin-like PCBs cannot be excluded (Knerr and Schrenk 2006). For this reason, some scientists have suggested that the carcinogenic evaluation

of PCBs based solely on PCB TEQ evaluation is not sufficient (Safe 1994). Research and debate is active on the most appropriate methods to evaluate carcinogenic potential of environmental PCB mixtures.

The contribution of dioxin-like and non-dioxin-like PCBs to non-cancer effects is also an area of active research and discussion. Unlike carcinogenicity, health risks from PCBs associated with these effects are not evaluated on a TEQ basis. For these endpoints, non-dioxin-like PCBs may play a greater role than they do in carcinogenicity. The mechanisms of action for PCB neurotoxicity are not thought to be mediated by the Ah receptor, suggesting that non-dioxin-like PCBs may be important. However, the specific PCB congeners involved have not been well-characterized. It is possible that the most potent congeners for these endpoints may be enhanced or diluted in environmental mixtures relative to mixtures used to develop toxicity metrics. For example, environmental mixtures of PCBs may have more- or less-potent immunological effects than do the Aroclor 1254 mixture used in the study that is the basis for the reference dose.

Toxicological Profiles for All Other Chemicals of Potential Concern

1. 1,2-DIPHENYLHYDRAZINE

1,2-Diphenylhydrazine is a white solid that is only slightly soluble. It adheres to soil and can be carried into the air along with windblown dust. Once in water or exposed to air it is transformed into other chemicals within minutes, including azobenzene and benzidine. 1,2-Diphenylhydrazine is used to make fabric dyes in other countries, and to make certain medicines. There are no other major anthropogenic or natural sources of 1,2-diphenylhydrazine (ATSDR 1990).

Pharmacokinetics

Pharmacokinetic studies of 1,2-diphenylhydrazine have not been conducted with humans. Soil particles contaminated by this compound may be inhaled or ingested, but it is likely that most of the chemical would be excreted via urine (ATSDR 1990).

Acute toxicity

The acute health effects of 1,2-diphenylhydrazine in humans have not been studied. Animals die if they swallow large amounts of 1,2-diphenylhydrazine (ATSDR 1990).

Chronic toxicity

Animals develop liver disease if they eat small amounts of 1,2-diphenylhydrazine for more than a year (ATSDR 1990). Chronic toxicity data for humans are not available.

Carcinogenicity

EPA has determined that 1,2-diphenylhydrazine is a probable carcinogen (B2) because it causes cancer in rats and mice that have eaten it in food for most of their lifetime. EPA has established an **oral cancer slope factor of 0.8 per mg/kg-day** (IRIS).

2. 1,3-DICHLOROBENZENE AND 1,4-DICHLOROBENZENE

1,3-Dichlorobenzene is a clear liquid used to make herbicides, insecticides, medicine, and dyes. 1,4-Dichlorobenzene is a clear to white solid with a strong, pungent odor. When exposed to air, it slowly evaporates from a solid to a vapor. Most people can smell 1,4-dichlorobenzene in the air at very low levels. 1,4-Dichlorobenzene is the more common of the two chemicals. Dichlorobenzenes do not dissolve easily in water, and the small amounts that enter water quickly evaporate into the air. Sometimes, dichlorobenzenes bind to soil and sediment. Dichlorobenzenes in soil usually are not easily broken down by soil organisms. Evidence suggests that plants and fish absorb dichlorobenzenes (ToxFAQs).

Pharmacokinetics

Very little is known about the health effects of 1,3-dichlorobenzene, especially in humans, but they are likely to be similar to those of 1,4-dichlorobenzene (ToxFAQs). Pharmacokinetic information for oral 1,4-diclorobenze exposure is very limited, although the liver and kidney have been identified as target organs (IRIS).

Acute toxicity

Dichlorobenzenes have low acute toxicity. Nausea and vomiting are common, while liver damage is a rare effect after large exposures. Ingestion may result in hemolytic anemia, jaundice, and methemoglobinemia. Irritation of nose and eyes may be caused by exposure to vapors. CNS depression has been observed when airborne concentrations become extremely objectionable to the eyes and nose. The solid material produces a sensation of warmth or burning when held in contact with the skin, but the resulting irritation is slight; warm fumes or strong solutions of dichlorobenzene may irritate the intact skin slightly on prolonged or repeated contact (HSDB).

Chronic toxicity

Dichlorobenzene may cause liver damage and, in severe cases, cirrhosis. Individuals who are exposed to higher concentrations of p-dichlorobenzene may show weakness, dizziness, headache, rhinitis, twitching of the facial muscles, weight loss, and acute hemolytic anemia with methemoglobinuria (HSDB). NCEA has developed **RfDs of 0.003 and 0.03 mg/kg-day for 1,3-dichlorobenzene and 1,4-dichlorobenzene, respectively** (EPA 2005).

Carcinogenicity

Although there is inadequate evidence in humans for the carcinogenicity of dichlorobenzenes, there is sufficient evidence in animal models to determine the carcinogenicity of 1,4-dichlorobenzene. 1,4-Dichlorobenzene was shown to cause a high incidence of liver tumors in male and female mice. Evidence that its mechanism of action of carcinogenesis in the liver may be relevant for humans supports the IARC ruling that 1,4-dichlorobenzene is possibly carcinogenic to humans (Group 2B). The carcinogenicity of 1,3-dichlorobenzene has not been assessed by IARC due to a lack of human and animal studies on the topic (ToxFAQs). An **oral cancer slope factor of 0.024 per mg/kg-day** was developed by NCEA for 1,4-dichlorobenzene (EPA 2005).

3. 2,4,6-TRICHLOROPHENOL

Chlorophenols are a group of chemicals that are created by adding chlorines to a phenol molecule. Phenol is an aromatic compound derived from benzene. There are 5 basic types of chlorophenols and 19 different chlorophenols. Most are solid at room temperature with a strong, medicinal taste and smell. Even very small amounts may be tasted in water.

Some chlorophenols are used as pesticides while others are used in antiseptics. Small amounts are produced as a byproduct of water disinfection with chlorine. Significant amounts may also be released to the environment if the water or wastewater undergoing chlorination contains phenol (HSDB). Chlorophenols are also produced by paper mills while bleaching wood pulp with chlorine to make paper. Chlorophenols enter the environment when they are created as byproducts of disinfection or bleaching or during manufacture and use of pesticides and herbicides such as Prochloraz and Chloranile. Chloranile is currently used as a bleaching agent, but was previously used as a defoliant, herbicide and fungicide. Chlorophenols are generally released into the environment via water, and are rarely released into the air. Airborne chlorophenols are broken down by sunlight and then washed out of the sir by rain. Chlorophenols stick to soil and sediments at the bottom of lakes, streams, and rivers. Micro-organisms break down and remove low levels of chlorophenols in water, soil, and sediment from the environment in a few days to weeks (ToxFAQs).

Pharmacokinetics

A Finnish study of sawmill workers with occupational exposure to 2,4,6-trichlorophenol showed that it is readily absorbed across the skin and through the mucous membranes of the lungs. The mechanism of action of 2,4,6-trichlorophenol is interference with metabolism, which prevent cells from producing energy (HSDB).

Acute toxicity

Redness and edema result from dermal contact. If contact is prolonged, moderate and severe chemical burns may occur. 2,4,6-Trichlorophenol is also a lung and eye irritant (HSDB).

Chronic toxicity

Long-term exposure to this chemical results in reduced lung function, and possibly pulmonary fibrosis (HSDB). NCEA has developed an **oral RfD of 0.0001 mg/kg-day** for 2,4,6-trichlorophenol (EPA 2004).

Carcinogenicity

Although there is no human data available, sufficient animal studies have been conducted to classify 2,4,6-trichlorophenol in group 2B, a probable human carcinogen (IARC). Increased incidences of lymphomas or leukemia were observed in male rats and tumors in the livers of male and female mice (HSDB). EPA established an **oral cancer slope factor of 0.011 per mg/kg-day** for 2,4,6-trichlorophenol (IRIS).

4. 2,4-DICHLOROPHENOL

Chlorophenols are a group of chemicals that are created by adding chlorines to a phenol molecule. Phenol is an aromatic compound derived from benzene. There are 5 basic types of chlorophenols and 19 different chlorophenols. Most are solid at room temperature with a strong, medicinal taste and smell. Even very small amounts may be tasted in water.

Some chlorophenols are used as pesticides while others are used in antiseptics. Small amounts are produced as a byproduct of water disinfection with chlorine. Significant amounts may also be released to the environment if the water or wastewater undergoing chlorination contains phenol (HSDB). Chlorophenols are also produced by paper mills while bleaching wood pulp with chlorine to make paper. Chlorophenols enter the environment when they are created as byproducts of disinfection or bleaching or during manufacture and use of pesticides and herbicides such as Prochloraz and Chloranile. Chloranile is currently used as a bleaching agent, but was previously used as a defoliant, herbicide and fungicide. Chlorophenols are generally released into the environment via water, and are rarely released into the air. Airborne chlorophenols are broken down by sunlight and then washed out of the sir by rain. Chlorophenols stick to soil and sediments at the bottom of lakes, streams, and rivers. Micro-organisms break down and remove low levels of chlorophenols in water, soil, and sediment from the environment in a few days to weeks (ToxFAQs).

Pharmacokinetics

2,4-Dichlorophenol (DCP) has been shown to disrupt metabolism in rats. It has a demonstrated half-life in these animal models of 4 to 30 minutes, meaning that it does not build up in the body before it is excreted in urine (HSDB).

Acute toxicity

Acute exposures may cause muscular weakness, gastroenteric disturbances, severe depression, and collapse. 2,4-DCP primarily affects the nervous system, but it may also cause edema of the lung and injury to the liver, pancreas and spleen. Contact

dermatitis may be seen as well. Additional chlorination of the chemical increases its toxicity (HSDB).

Chronic toxicity

Chronic exposure may result in chloracne (HSDB). EPA has developed an **RfD of 0.003 mg/kg-day for 2,4-dichlorophenol** (IRIS).

Carcinogenicity

IARC states that combined exposure to polychlorophenols or to their sodium salts is possibly carcinogenic to humans, and ranks them in Group 2B. There is evidence to suggest that people exposed to chlorophenols for a long time may have slightly higher incidences of cancer. However, the people studied were exposed to other chemicals as well, so no definite link can be made between exposure to chlorophenol and increased incidence of cancer (HSDB).

5. 2,4-DINITROPHENOL

Dinitrophenols are a group of manufactured chemicals that do not exist naturally in the environment. There are six different dinitrophenols. The most commonly found and most commercially important dinitrophenol, 2,4-dinitrophenol (DNP), is a yellow solid with no smell. It is used to make dyes, wood preservatives, explosives, insect control substances, and other chemicals. It is also used in the process of developing photographic film. Currently, exposure to dinitrophenols occurs mainly from breathing air, drinking water, or eating food that contains the chemicals. Before being banned in 1938, DNP was used in diet pills. The majority of the information on the health effects of dinitrophenols comes from studies of patients who were prescribed diet pills containing DNP before it was banned (ToxFAQs).

When DNP enters the environment, it dissolves only slightly in water, and will not easily evaporate to air. It can be broken down slowly in water and soil by small organisms or through reactions with other chemicals. DNP sticks to small particles in water, which will cause it to eventually settle to the bottom sediment. Because DNP also sticks to some types of soil particles, it does not usually migrate deep into the soil with rainwater (ToxFAQs).

Pharmacokinetics

DNP acts as a stimulant to increases metabolic rate which then causes the body to increase temperature, heart and breathing rates. DNP is metabolized by humans, dogs, and mice into various phenolic compounds which are excreted through urine (HSDB).

Acute Toxicity

The dose of dinitrophenols ingested that will cause harmful effects varies among people. Increased basal metabolic rate (the rate that you use energy at complete rest), increased sweating, extreme thirst, a feeling of warmth, increased heart rate, breathing

rate, and body temperature have all been observed in people who swallowed as little as 1 mg/kg-day or as much as 46 mg/kg-day for short or long periods of time. Ingestion may cause stimulation or excitement, followed by marked fatigue and depression (HSDB).

Chronic Toxicity

Ingesting 2-4 mg/kg-day DNP for short or long periods has caused cataracts in some people, while ingesting 1 to 4 mg/kg-day for short or long periods has caused skin rashes and decreases in white blood cells. A significant decrease in white blood cell count may prevent the immune system from functioning properly. Similar doses have also been observed to cause weight loss. Cyanosis and jaundice caused by liver damage have been observed both in individuals exposed for long periods of time and in those surviving the acute phase of poisoning (HSDB). EPA has developed an **RfD of 0.002 mg/kg-day** for DNP based on human exposures and studies conducted with animals (IRIS).

Carcinogenicity

Currently, there are no studies available in people or animals on the carcinogenic effects of DNP. Due to this lack of data, the Department of Health and Human Services (DHHS), the International Agency for Research on Cancer (IARC), and the EPA have not classified DNP for carcinogenicity (IRIS, ToxFAQs).

6. 2,4-DINITROTOLUENE AND 2,6-DINITROTOLUENE

Both 2,4-dinitrotoluene (DNT) and 2,6-DNT are pale yellow solids with a slight odor. They are two of the six forms of DNT. DNT is not a natural substance, and it is created by mixing toluene with nitric acid. DNT is usually used to make flexible polyurethane foams used in the bedding and furniture industries. It is also used in the air bags of automobiles and in the production of explosives, ammunition, and dyes.

DNT is present in the environment in many media, including soil, surface and ground water, and air. It has been found at some hazardous waste sites that contain buried ammunition wastes; however, it is found mostly in the air outside of certain manufacturing plants.

DNT does not usually evaporate, and it does not stay in the environment because it is broken down by sunlight and by bacteria. In water, DNT tends to be more stable and less likely to break down. DNT can be transferred to plants by root uptake from contaminated water or soil (ToxFAQs).

Pharmacokinetics

The human health effects from DNT exposure that have been reported are from occupational exposure studies in which workers were exposed primarily by inhalation, but with some contribution assumed from dermal absorption and ingestion. Humans appear to metabolize DNT fairly quickly with rapid absorption

followed by urinary excretion of metabolites. A similar pattern of metabolism has been observed in animal models (HSDB).

Acute toxicity

The following symptoms have been reported as a result of varying doses of DNT: vertigo, fatigue, dizziness, weakness, nausea, vomiting, insomnia, tremor, paralysis, unconsciousness, chest pain, shortness of breath, palpitation, anorexia, and loss of weight. Following poisoning, the following symptoms have been observed: methemoglobinemia, anemia and liver necrosis. Liver injury may be more common than cyanosis (HSDB).

Chronic toxicity

Major effects from chronic exposure include methemoglobinemia, cyanosis; neurotoxicity; and possible excess mortality from ischemic heart disease and residual circulatory system effects. Neurotoxicity is characterized by vertigo, tremors, unconsciousness, and paralysis (HSDB). EPA has developed an **RfD of 0.002 mg/kg-day** for 2,4-DNT based on animal studies as well as human exposures (IRIS). For 2,6-DNT, a HEAST **RfD of 0.001 mg/kg-day** is available (EPA 2004).

Carcinogenicity

In animal studies, both 2,4-DNT and 2,6-DNT caused liver cancer in rats. There are no studies on the effects of 2,4-DNT and 2,6-DNT on people. The International Agency for Research on Cancer (IARC) has determined that 2,4-DNT and 2,6-DNT are possible human carcinogens (ToxFAQs). An **oral cancer slope factor of 0.68 mg/kg-day** has been developed for a mixture of 2,4-DNT and 2,6-DNT (IRIS).

7. 2-CHLOROPHENOL

Chlorophenols are a group of chemicals that are created by adding chlorines to a phenol molecule. Phenol is an aromatic compound derived from benzene. There are 5 basic types of chlorophenols and 19 different chlorophenols. Most are solid at room temperature with a strong, medicinal taste and smell. Even very small amounts may be tasted in water.

Some chlorophenols are used as pesticides while others are used in antiseptics. Small amounts are produced as a byproduct of water disinfection with chlorine. Significant amounts may also be released to the environment if the water or wastewater undergoing chlorination contains phenol (HSDB). Chlorophenols are also produced by paper mills while bleaching wood pulp with chlorine to make paper. Chlorophenols enter the environment when they are created as byproducts of disinfection or bleaching or during manufacture and use of pesticides and herbicides such as Prochloraz and Chloranile. Chloranile is currently used as a bleaching agent, but was previously used as a defoliant, herbicide and fungicide. Chlorophenols are generally released into the environment via water, and are rarely released into the air. Airborne

chlorophenols are broken down by sunlight and then washed out of the sir by rain. Chlorophenols stick to soil and sediments at the bottom of lakes, streams, and rivers. Micro-organisms break down and remove low levels of chlorophenols in water, soil, and sediment from the environment in a few days to weeks (ToxFAQs).

Pharmacokinetics

2-Chlorophenol disrupts metabolism, and may increase heart and breathing rates before it is excreted through bile and urine (HSDB).

Acute toxicity

Acute exposures may cause muscular weakness, gastroenteric disturbances, severe depression, and collapse. 2-Chlorophenol primarily affects the nervous system, but it may also cause edema of the lung and injury to the liver, pancreas and spleen. Contact dermatitis may be seen as well. Additional chlorination of the chemical increases its toxicity (HSDB).

Chronic toxicity

Chronic exposure may result in chloracne (HSDB). EPA has developed an **RfD of 0.005 mg/kg-day for 2-chlorophenol** (IRIS).

Carcinogenicity

Carcinogenicity of 2-chlorophenol is unknown, EPA has not completed its evaluation for carcinogenic potential of this chemical. There is evidence to suggest that people exposed to chlorophenols for a long time may have slightly higher incidences of cancer. However, the people studied were exposed to other chemicals as well (ToxFAQs).

8. 3,3'-DICHLOROBENZIDINE

3,3'-Dichlorobenzidine is a gray- to purple-colored crystalline solid. It changes from a solid to a gas very slowly. The salt of this compound is the major form in actual use. Neither 3,3'-dichlorobenzidine nor its salt are found naturally in the environment. They are manufactured for pigments for printing inks, textiles, plastics and enamels, paint, leather, and rubber. Human exposure may occur in industrial settings via inhalation or direct contact, or in residential settings through contact with contaminated dirt or water.

Pharmacokinetics

When 3,3'-dichlorobenzidine enters the body, very little of it leaves the body unchanged. Over 90% of the parent compound is transformed to metabolites which leave the body, mainly in urine and to a lesser extent in feces, within 72 hours after exposure (ToxFAQs).

Acute toxicity

The salt form of 3,3'-dichlorobenzidine may have caused sore throat, respiratory infections, stomach upset, headache, dizziness, caustic burns, and dermatitis in workers exposed to the chemical. Death has occurred in laboratory animals that ate very high levels of 3,3'-dichlorobenzidine mixed in their food for short periods of time (ToxFAQs).

Chronic toxicity

IRIS does not provide a discussion of chronic effects of exposure to 3,3′-dichlorobenzidine or an RfD. Laboratory animals exposed to moderate levels of 3,3'-dichlorobenzidine mixed with food for a long time suffered mild injury to the liver (ToxFAQs).

Carcinogenicity

Studies show that 3,3'-dichlorobenzidine caused cancer of the liver, skin, breast, bladder, and tissues that form blood and other organs in laboratory animals that ate it in their food (ToxFAQs). To date, evidence is inconclusive with regard to whether 3,3'-dichlorobenzidine has caused cancer in people who worked with it or who were exposed to it unknowingly or by accident for a short or long time. However, because of the many types of cancer that 3,3'-dichlorobenzidine has caused in different tissues of many types of laboratory animals, 3,3'-dichlorobenzidine has been classified as a probable human carcinogen (B2) with an **oral cancer slope factor of 0.45 per mg/kg-day** (IRIS).

9. 3-NITROANILINE AND 4-NITROANILINE

Nitroaniline may be released to the environment from process and waste emissions involved in its production or use as a chemical intermediate and through stack emissions from hazardous waste incineration. Once in the environment, it has a half life of approximately one day in the air, and four days in water. Nitroaniline persists for the longest time in soil, where it binds to particles and is prevented from mobilizing. Exposure to sunlight will break down the chemical (HSDB).

Pharmacokinetics

Nitroaniline is quickly absorbed across the skin and through the lining of the lungs. It has a biological half-life of approximately 1 hour, and is excreted largely through urine (HSDB).

Acute Toxicity

Nitroaniline may be harmful if absorbed through skin or inhaled. It is absorbed rapidly and induces methemoglobinemia. Symptoms of methemoglobinemia include cyanosis, headache, dizziness, weakness, lethargy, loss of coordination, dyspnea, coma, and death. Heart, liver, and kidney effects may be secondary to hemolysis.

Other symptoms of overexposure include irritability, vomiting, diarrhea, cyanosis, ataxia, tachycardia, convulsions, respiratory arrest, and anemia (HSDB).

Chronic Toxicity

Nitroaniline is a potent methemoglobin-inducing agent and given sufficiently high or prolonged exposures, hemolysis can occur. Liver damage is also a known effect of nitroaniline exposure, and prolonged exposure may also result in heart or kidney damage (HSDB). EPA has developed **provisional RfDs of 0.0003 mg/kg-day and 0.003 mg/kg-day for 3-nitroaniline and 4-nitroaniline, respectively** (EPA 2005).

Carcinogenicity

Nitroaniline was found to be not classifiable as to carcinogenicity by IARC (HSDB). EPA's PPRTV provides a **provisional oral cancer slope factor of 0.021 per mg/kg-day** for both 3-nitroaniline and 4-nitroaniline (EPA 2005).

10. 4,6-DINITRO-O-CRESOL

Dinitrocresols are manufactured chemicals that do not exist naturally in the environment. There are 18 different dinitrocresols of which 4,6-dinitro-o-cresol (DNOC) is the most commercially important. In its pure form, DNOC is a yellow solid with no smell that stains human skin on contact. Used primarily for insect control and crop protection, DNOC may be sold under several trade names including Antinonnin, Detal, and Dinitrol (ToxFAQs).

DNOC enters the environment during its manufacture and use, and is occasionally formed through reactions with other airborne chemicals. Another path for DNOC to enter the environment is through leaks at landfills, or accidental spills that occur during manufacture or transport.

Once in the environment, DNOC will only dissolve slightly in water, and it does not evaporate easily into air. DNOC will adhere to suspended particles in water, eventually settling to the bottom of lakes and streams. Because of its tendency to adhere to particles, DNOC does not usually migrate through soil to groundwater. Small organisms present in air, water and soil slowly break DNOC down (ToxFAQs).

Pharmacokinetics

DNOC is a yellow compound that. Absorption of DNOC by any route and subsequent distribution to tissues results in a characteristic yellow staining of visceral organs and tissues including the eyes, blood serum, skeletal tissues, and urine. The mechanism of acute toxicity is disruption of metabolism and diversion of energy into heat production which leads to an increase in body temperature (HSDB).

Blood levels of DNOC below 10 ppm are considered of trivial importance; levels of 11 to 20 ppm indicate appreciable absorption; and above these blood levels toxic

manifestations are likely. Levels greater than 50 ppm are critically dangerous (Doull et al. 1986).

Acute toxicity

Acute poisoning may result in increased basal metabolic rate, including increased temperature, heart and breathing rates. Other symptoms of exposure include nausea, gastric upset, restlessness, sensation of heat, flushed skin, sweating, rapid respiration, increased pulse rate, tachycardia, fever, cyanosis, and finally collapse and coma (ToxFAQs, HSDB).

Chronic toxicity

Chronic exposure to DNOC may cause increased basal metabolic rate, feelings of fatigue, restlessness, or anxiety, excessive sweating, unusual thirst, and loss of weight. A yellow staining of the whites of the eyes has been noted, and cataract formation is another possible result of chronic DNOC exposure (ToxFAQs, HSDB). EPA has established a **provisional RfD of 0.0001 mg/kg-day** for 4,6-dinitro-o-cresol (EPA 2004).

Carcinogenicity

DNOC is not rated by IARC, EPA or DHHS. Its carcinogenicity has not been classified, as studies have not been conducted to determine carcinogenic potential in humans or animals (ToxFAQs, IRIS).

11. 4-CHLOROANILINE

4-Chloroaniline or para-chloroaniline (PCA) is a colorless to amber-colored crystalline solid with a slight aromatic odor. The chemical is soluble in water and in common organic solvents. PCA is used as an intermediate in the production of a number of products, including agricultural chemicals, azo dyes and pigments, cosmetics, and pharmaceutical products (HSDB).

Pharmacokinetics

In humans, damage to hemoglobin molecules and a reduced ability to circulate oxygen throughout the body is detectable as early as 30 minutes after accidental exposure, with a maximum level at 3 hours. Due to common genetic differences in how humans metabolize chemical compounds, certain individuals may be at greater risk from exposure. Excretion in humans occurs primarily via the urine, with PCA and its conjugates appearing as early as 30 minutes after exposure. Excretion takes place mainly during the first 24 hours and is almost complete within 72 hours. Repeated exposure to PCA leads to cyanosis and methemoglobinemia, followed by effects in blood, liver, spleen, and kidneys (HSDB).

Acute Toxicity

Exposure via inhalation and/or simultaneous dermal absorption may result in severe headache, nausea, vomiting, dryness of throat, confusion, ataxia, vertigo, lethargy, drowsiness, and finally coma. Many of these symptoms can be attributed to increased levels of methemoglobin (HSDB).

Chronic Toxicity

Long term exposure to PCA may result in the development of anemia or cyanosis. A Heart, liver, and kidney effects may be secondary to hemolysis (HSDB). EPA has developed an **RfD of 0.004 mg/kg-day** based on studies conducted with rats (IRIS).

Carcinogenicity

IARC states that there is inadequate evidence in humans for the carcinogenicity of PCA. However, because there is sufficient evidence in experimental animals for the carcinogenicity of PCA, it has been designated as a Group 2B chemical, ranking it as possibly carcinogenic to humans (ToxFAQs). EPA has not fully evaluated this chemical for carcinogenic potential (IRIS).

12. 4-METHYLPHENOL OR P-CRESOL

Cresols are a widely occurring natural and manufactured group of chemicals. In their pure form, they are colorless solids and may be liquids if they are mixtures. Cresols generally smell like medicine or tar. There are three forms of cresols that are only slightly different in their chemical structure: ortho-cresol (o-cresol), meta-cresol (m-cresol), and para-cresol (p-cresol). These forms may occur separately or as a mixture. They are used as solvents to dissolve other chemicals, as disinfectants and deodorizers, and are ingredients in various pesticides.

Cresols are found in many foods as well as in wood and tobacco smoke, crude oil, and coal tar. Cresols are also a main component of brown mixtures such as creosote and cresylic acids, which are wood preservatives. Small organisms in soil and water produce cresols when they break down materials in the environment. Cresols enter the environment from natural sources, car exhaust, combustion, manufacturing use, and waste sites. Cresols are ubiquitous in our environment, but usually occur only at low levels because they quickly break down. In air, cresols quickly break down into other chemicals. Cresols do not evaporate quickly from water, but they can be removed by bacteria. Cresols may persist longer when it reaches deep groundwater or water that does not have bacteria.

In soil, approximately one half of the total amount of cresols present will break down in a week. Cresols do not appear to accumulate in fish or meat.

Pharmacokinetics

Cresols are corrosive to tissues and can cause serious burns. These chemicals are rapidly absorbed by all routes, cause systemic effects, and can be fatal by any route of exposure. Systemic effects include profound CNS depression, seizures, hemolysis, methemoglobinemia, pulmonary edema, and lung, liver, pancreas, spleen, heart, and kidney damage. Metabolic acidosis may occur. Cresol is a cellular poison and is toxic to all cells (HSDB).

Acute Toxicity

Skin contact is the main exposure route. Pain is followed by numbness; skin reddens, then blanches, blisters, and forms a scab. Skin contact can result in severe skin burns. Eye contact produces irritation, redness, corneal burns, keratitis, and possibly, in severe cases, blindness.

Inhalation produces coughing and labored, fast breathing; respiratory failure may result. Ingestion causes a burning pain in the mouth and throat, and abdominal pain, nausea, vomiting, bloody diarrhea and collapse. White necrotic lesions of the mouth, throat and stomach are also seen (HSDB).

Chronic Toxicity

Short-term and long-term studies with animals have shown similar effects from exposure to cresols. No human or animal studies have shown harmful effects from cresols on the ability to have children.

It is not known what the effects are from long-term ingestion or skin contact with low levels of cresols (ToxFAQs). Chronic exposure may produce allergic dermatitis, digestive disturbances, CNS effects, and liver and kidney damage. Effects of chronic exposure to p-cresol may include vomiting, difficulty swallowing, excessive salivation, diarrhea, loss of appetite, headache, fainting, dizziness, mental disturbances, skin rash, or death from severe damage to the liver or kidneys (HSDB). HEAST has developed an **RfD of 0.005 mg/kg-day** for 4-methylphenol (EPA 2005).

Carcinogenicity

4-methylphenol has received classification as a class C chemical (a possible human carcinogen) from IARC. This ruling was based on limited evidence from animal studies, as the data from human exposures is inadequate (HSDB).

13. ALDRIN

Aldrin is the common name for a popular insecticide that was used extensively until 1970, at which time the US Department of Agriculture cancelled all uses. In 1972, however, EPA approved aldrin for killing termites. Use of aldrin to control termites continued until 1987, at which time the manufacturer voluntarily canceled the registration for use in controlling termites. Pure aldrin is a white powder, but

technical-grade aldrin (>85% aldrin) is a tan powder. Aldrin slowly evaporates in the air.

Pharmacokinetics

Exposure of the general population to aldrin most likely occurs through eating contaminated food. Exposure of some infants occurs by drinking mother's milk containing aldrin. Studies in animals show that aldrin enters the body quickly after exposure. Once inside the body, aldrin quickly breaks down to dieldrin, where it is stored in lipid reserves.

Acute toxicity

Exposure to very high levels of aldrin for a short time causes convulsions or kidney damage. One very young child died from drinking a solution containing a very high level of dieldrin. Another very young child died after eating food contaminated with aldrin (ToxFAQs). Animal studies have shown that exposure to moderate levels of aldrin for a short time causes decreased ability to fight infections.

Chronic toxicity

Exposure to moderate levels of aldrin for a long time causes headaches, dizziness, irritability, vomiting, or uncontrollable muscle movements. Some sensitive people develop a condition in which aldrin or dieldrin causes the body to destroy its own blood cells (ToxFAQs).

EPA established an **RfD of 0.00003 mg/kg-day** based on observed liver toxicity in a chronic rat feeding study (IRIS).

Carcinogenicity

EPA has classified aldrin as a probable human carcinogen (B2) and has established an **oral cancer slope factor of 17 per mg/kg-day** based on observations of significant increases in tumor responses in three different strains of mice in both males and females following aldrin exposure (IRIS).

14. ALUMINUM

Aluminum is the most abundant metal and the third most abundant element, after oxygen and silicon, in the earth's crust. It is widely distributed and constitutes approximately 8 percent of the earth's surface layer. However, aluminum is a very reactive element and is never found as free metal in nature. It is found combined with other elements, most commonly with oxygen, silicon, and fluorine. High concentrations in the environment can be caused by the mining and processing of its ores and by the production of aluminum metal, alloys, and compounds. Small amounts of aluminum are released into the environment from coal-fired power plants and incinerators (ATSDR 1999b).

Pharmacokinetics

Since little aluminum is absorbed, it is excreted in the feces, much of it in the form of aluminum phosphate. There is no generally no increase in the amount of aluminum in tissues, except in bone, as demonstrated in animal experiments. Some aluminum may be absorbed by patients undergoing dialysis; the kidney is responsible for removing the majority of absorbed aluminum (HSDB). Aluminum in lung tissue appears to be derived from inhaled particulates rather than any affinity of lung tissue for aluminum.

Acute toxicity

Low-level exposure to aluminum from food, air, water, or contact with skin is not thought to harm your health (ATSDR 1999b). Aluminum, however, is not a necessary substance for our bodies and too much may be harmful. People who are exposed to high levels of aluminum in air may have respiratory problems including coughing and asthma from breathing dust.

Chronic toxicity

Some studies show that people with Alzheimer's disease have more aluminum than usual in their brains. Data are inconclusive on whether aluminum causes the disease or whether the buildup of aluminum happens to people who already have the disease. Aluminum is known to cause additional neurological problems such as memory loss and impaired motor skills. Infants and adults who received large doses of aluminum as a treatment for another problem developed bone diseases, which suggests that aluminum may cause skeletal problems. Some sensitive people develop skin rashes from using aluminum chlorohydrate deodorants (ATSDR 1999b). EPA's PPRTV provides an **RfD for aluminum of 1 mg/kg-day** (EPA 2004).

Carcinogenicity

EPA has not conducted a complete evaluation and determination of the carcinogenicity of aluminum (IRIS). Available data suggest that this element is not carcinogenic (ATSDR 1999b).

15. ANILINE

Aniline is a clear to slightly yellow liquid with a characteristic odor. It does not readily evaporate at room temperature, is slightly soluble in water, and mixes readily with most organic solvents. Aniline is used to make a wide variety of products such as polyurethane foam, agricultural chemicals, synthetic dyes, antioxidants, stabilizers for the rubber industry, herbicides, varnishes and explosives. Aniline in the air is broken down within a few days by other chemicals and by sunlight. In water, it can stick to sediment and particulate matter or evaporate to the air. Most of it will be broken down by bacteria and other micro-organisms. Aniline will only partially stick to the soil. Small amounts may evaporate into air or pass through the soil to groundwater. Most

of the aniline in soil will be broken down by bacteria and other micro-organisms. Aniline does not accumulate in the food chain (ToxFAQs).

Pharmacokinetics

Humans appear to be more sensitive than rats to aniline exposure (as indicated by formation of methemoglobin) Jenkins et al. (1972) noted that after oral administration of aniline to volunteers and rats, the dose that produced increased levels of methemoglobin was much lower for humans than for rats. The reason for this increased sensitivity in humans is not known and does not appear to be related to the half-life of methemoglobin in the serum, which is three times longer in rats than in humans. Human half-life of methemoglobin is less than one hour (IRIS).

Acute Toxicity

Aniline can be toxic if it is ingested, inhaled, or contacts the skin. Aniline damages hemoglobin, a protein that normally transports oxygen in the blood. The damaged hemoglobin cannot carry oxygen. This condition is known as methemoglobinemia and its severity depends on how much a person is exposed to and for how long. Methemoglobinemia is the most prominent symptom of aniline poisoning in humans, resulting in cyanosis (a purplish blue skin color) following acute high exposure to aniline. Dizziness, headaches, irregular heart beat, convulsions, coma, and death may also occur. Direct contact with aniline can also produce skin and eye irritation (ToxFAQs).

Chronic Toxicity

Long-term exposure to lower levels of aniline may cause symptoms similar to those experienced in acute high-level exposure. There is no reliable information on whether aniline has adverse reproductive effects in humans. Studies in animals have not demonstrated reproductive toxicity for aniline (ToxFAQs). A provisional EPA **RfD of 0.007 mg/kg-day** was used in this HHRA (EPA 2005).

Carcinogenicity

Evidence from human studies is inadequate to determine whether exposure to aniline can increase the risk of developing cancer in people. Rats that ate food contaminated with aniline for life developed cancer of the spleen. The International Agency for Research on Cancer (IARC) determined that aniline is not classifiable as to its carcinogenicity to humans. The EPA has determined that aniline is a probable human carcinogen (ToxFAQs). EPA has established an **oral cancer slope factor of 0.0057 mg/kg-day** (IRIS).

16. ANTIMONY

Antimony is naturally present in the earth's crust. The release of antimony into the environment occurs primarily through anthropogenic sources like non-ferrous metal

mining, smelting, refining, and production, the use and disposal of antimony alloys and compounds, coal combustion, and refuse and sludge combustion. Antimony exposure occurs through inhalation, ingestion of food containing antimony, and through dermal contact (IRIS).

Pharmacokinetics

Antimony is absorbed by erythrocytes and distributed to other tissues such as liver, adrenals, spleen, and thyroid. Much of the absorbed antimony is excreted via urine and feces. Of the antimony that is not excreted, the longest biological half-life is believed to occur in the lungs. The highest concentrations of antimony after acute or chronic exposure have been found in the thyroid, adrenals, liver, and kidney (HSDB).

Acute toxicity

Violent vomiting, diarrhea, lowered respiratory rate, myocardial edema, hyperemia, and capillary engorgement are major results of acute exposure to antimony. Seventy people became acutely ill after ingesting lemonade containing 0.013% antimony. Fifty-six of the victims were treated for burning stomach pains, colic, nausea, and vomiting. Most recovered after approximately three hours, while some required hospitalization for a few days (IRIS).

Chronic toxicity

Dyspnea, weight and hair loss, popular eruptions on the skin, jaundice, damage to the heart and liver, and spleen, kidney damage, abnormal increase in erythrocytes, and a decrease in leukocytes are reported from long-term exposure to antimony. Chronic inhalation results in damage to the lungs, liver and heart (HSDB). EPA developed an **RfD for antimony of 0.0004 mg/kg-day** based on a study in which rats were exposed to potassium antimony tartrate (IRIS).

Carcinogenicity

EPA has not conducted a complete evaluation and determination of the carcinogenicity of antimony (IRIS).

17. BARIUM

Barium metal does not occur in nature. The most common barium ores are sulfate, barite, carbonate, and witherite. The largest use of barium is in the removal of traces of gases from vacuum and television picture tubes. Barium is released into the environment through the disposal of drilling waste, copper smelting, manufacture of motor vehicle parts, combustion of coal and oil, and the mining, refining, and production of barium and barium-based chemicals (OGWDW).

Pharmacokinetics

The human body contains approximately 22 mg of barium, 66% of which is in the bones. Common routes of exposure are ingestion, inhalation of dust or fumes, and skin or eye contact (HSDB).

Acute toxicity

Exposure to large quantities of barium can cause gastrointestinal disturbances and muscular weakness. No Health Advisories have been established for short-term exposure to barium (OGWDW).

Chronic toxicity

Chronic exposure to barium can cause hypertension (OGWDW). Populations with pulmonary diseases are especially at risk. Barium is not considered an industrial health hazard (HSDB). EPA has established an **oral RfD for barium of 0.2 mg/kg-day** (IRIS).

Carcinogenicity

No suitable bioassays or epidemiological studies are available to assess the carcinogenicity of barium (IRIS). EPA has placed barium in weight-of-evidence group D, not classifiable as to human carcinogenicity.

18. BENZIDINE

Benzidine may be released as emissions and in wastewater during its production and use as an intermediate in the manufacture of direct azo dyes. Large-scale manufacturing of benzidine in the US has been suspended since 1976. It is now produced in the US for domestic consumption only with strict regulations that it be maintained in isolated or closed systems that would limit its release (HSDB). Exposure to benzidine is primarily occupational via dermal adsorption, inhalation, and ingestion in workers connected with its production and conversion into direct azo dyes. The respiratory route is of major importance under some manufacturing conditions.

Pharmacokinetics

Absorbed doses of benzidine are rapidly transferred to the excretory organs, liver, gastrointestinal tract, kidney, and bladder. Half-lives determined experimentally range from 65 hr in rat to 88 hr in dogs (HSDB).

Acute toxicity

Ingestion of benzidine may produce nausea, vomiting, liver, and kidney damage (HSDB).

Chronic toxicity

Long-term exposure to benzidine has been shown to produce a spectrum of lesions of the epithelium of the urinary bladder, which may precede appearance of malignancy. Presence of visible or occult of blood in urine or the development of pain or difficulty in urinating may signal appearance of such lesions (HSDB). EPA has established an **RfD of 0.003 mg/kg-day** based on a chronic oral mouse bioassay (IRIS).

Carcinogenicity

EPA has classified benzidine as a known (Class A) carcinogen based on observations of increased incidence of bladder cancer and bladder cancer-related deaths in exposed workers. EPA has established an **oral cancer slope factor of 230 per mg/kg-day** (IRIS).

19. BIS(2-CHLOROETHYL)ETHER

Bis(2-chloroethyl)ether (BCEE) is a colorless nonflammable liquid with a strong, unpleasant odor. It does not occur naturally, but is manufactured for use in the production of pesticides and other chemicals. Limited amounts of BCEE will dissolve in water, and it also will slowly evaporate into air. In the environment, BCEE is broken down by bacteria in soil and water and by chemical reactions in the air, so it does not tend to persist for long periods (ToxFAQs).

Pharmacokinetics

BCEE enters the body easily after being swallowed in food or water, or after being inhaled in air. It may also enter by crossing the skin when dermal contact occurs. Once inside the body, BCEE is broken down to a number of different chemicals, and these are eliminated in the urine or the breath. Most BCEE that enters the body is removed in this way within two to three days, so BCEE does not tend to bioaccumulate (ToxFAQs).

Acute toxicity

People exposed to BCEE vapors report that it is highly irritating to the eyes and the nose. Animal studies show that BCEE vapors can cause severe injury to the lungs, and may lead to death (ToxFAQs).

Chronic toxicity

The chronic effects of BCEE on other organs (besides the lung) and body functions have not been well studied. It is not known if BCEE impairs reproduction or the development of fetuses (ToxFAQs). EPA has not established an RfD for BCEE.

Carcinogenicity

Mice given repeated doses of BCEE through the mouth developed liver tumors. This suggests that BCEE might cause cancer in humans, although no cases of cancer due to BCEE have been reported in people and BCEE was also not found to induce excess

cancer after feeding to rats. EPA has classified BCEE as a probable human carcinogen (B2) and has established an **oral cancer slope factor of 1.1 per mg/kg-day** based on positive carcinogenicity results in two strains of mice and evidence of mutagenicity (IRIS).

20. BIS(2-CHLOROISOPROPYL)ETHER

Bis(2-chloroisopropyl)ether is used primarily as a solvent in the manufacture of fats, waxes, and greases; as an extractant; in paint and varnish removers; in spotting and cleaning solutions; and in textile processing (HSDB). There is no evidence of commercial production of this compound within the US.

If released to water or moist soil, bis(2-chloroisopropyl)ether will hydrolyze rapidly based on an estimated hydrolysis half-life of < 38.4 sec in water. Therefore, biodegradation, bioconcentration in aquatic organisms and adsorption to soil and sediment are not expected to be significant fate processes (HSDB).

Pharmacokinetics

After single oral doses, bis-chloroisopropylether appeared to be readily absorbed by both female rats and monkeys (HSDB). With respect to the percentage of the radiolabeled administered dose recovered in the tissues and excreta, higher amounts of radioactivity were found in the fat (1.98%), urine (63.36%), feces (5.87%), and expired air (15.96%) of the rat compared to the monkey. The corresponding figures in the monkey were 0.78%, 28.61%, 1.19%, and 0%.

Acute toxicity

The acute toxicity of bis(2-chloroisopropyl)ether is not well-studied. Studies with rats exposed to an atmosphere saturated with bis(2-chloroisopropyl) ether exhibited signs of immediate eye irritation and lack of coordination; the maximum exposure time causing no death was 1 hr. When rats were exposed to 700 ppm, deaths occurred after 6 hr of exposure. Autopsy revealed slight lung irritation and moderate to severe liver damage (HSDB).

Chronic toxicity

EPA has established an **RfD of 0.04 mg/kg-day** based a chronic oral study with mice that documented a decrease in hemoglobin and possible red blood cell destruction (IRIS).

Carcinogenicity

There is limited evidence in experimental animals for the carcinogenicity of bis(2-chloroisopropyl)ether. The IARC (1995) indicated the carcinogenicity of this chemical to humans is not classifiable (Category 3). HEAST provides an oral cancer slope factor of **0.07 per mg/kg-day for bis(2-chloroisopropyl)ether** (EPA 2005).

21. BIS(2-ETHYLHEXYL)PHTHALATE

Bis(2-ethylhexyl)phthalate (BEHP) is a man-made chemical that is commonly added to plastics to make them flexible. This compound is present in plastic products such as rainwear, footwear, upholstery materials, imitation leather, waterproof gloves, tablecloths, shower curtains, food packaging materials, floor tiles, and children's toys. It can be an ingredient in paints, flexible tubing, plastic bags, containers for blood, printing inks, pesticides, cosmetics, and vacuum pump oil and can be used for testing air filtration systems.

Pharmacokinetics

Small amounts of BEHP may enter your body by skin contact with plastics, but most evidence indicates that very little enters this way (ToxFAQs). Most BEHP that enters the body in food, water, or air is taken up into the blood from the intestines and lungs. After BEHP is absorbed into your body, most of it is rapidly broken down to mono(ethylhexyl)phthalate (MEHP) and 2-ethylhexanol. The toxicities of MEHP and 2-ethylhexanol are similar to the toxicity of BEHP. These compounds travel through the bloodstream to the liver, kidneys, and testes, and small amounts will become stored in fat or secreted in breast milk. Most of the BEHP, MEHP, and 2-ethylhexanol leave your body within 24 hours in the urine and feces.

Acute toxicity

BEHP appears to affect rats and mice more than it affects humans and some other animals. Short-term exposures to high levels of BEHP interfered with sperm formation in mice and rats. These effects were reversible, but sexual maturity was delayed when the animals were exposed before puberty. Short-term exposures appeared to have no effect on male fertility (ToxFAQs).

Chronic toxicity

Long-term exposure of rats to BEHP resulted in structural and functional changes in the kidney. The structural kidney changes seen in rats are similar to those in the kidneys of long-term dialysis patients (ToxFAQs).

EPA has established an **RfD of 0.02 mg/kg-day** based on a sub-chronic to chronic bioassay with guinea pig that documented increased relative liver weight (IRIS).

Carcinogenicity

EPA has classified BEHP as a probable human carcinogen (B2) and has established an **oral cancer slope factor of 0.014 per mg/kg-day** based on observations of significant dose-related increases in liver tumor responses in rats and mice of both sexes (IRIS).

22. BUTYL BENZYL PHTHALATE

Butyl benzyl phthalate (BBP) is a clear oily liquid that is used as a plasticizer mainly in the polyvinyl chloride for vinyl floor tile, vinyl foams and carpet backing and in

cellulose plastics and polyurethane (HSDB). It can exist in both the vapor and particulate phase when exposed to air, and will evaporate from water and moist soils. The half life of BBP is between four and thirteen days (HSDB).

Pharmacokinetics

No evidence was found describing the metabolism pathway of BBP in humans. In animal models it has been shown to absorb quickly across the walls of the intestine, and has a half life of 10 minutes in rats (Eigenberg et al. 1986). In general, phthalate esters are not absorbed through skin (Clayton and Clayton 1981) (HSDB).

Acute toxicity

No human data is available from controlled studies, however, observations of workers exposed in occupational settings has shown that the acute toxicity of phthalates is very slight and decreases generally with the increasing molecular weight (HSDB).

Chronic toxicity

Available data in humans are inadequate to serve a basis for assessment of effects of long term exposure to butyl benzyl phthalate in human populations (HSDB). EPA has established an **RfD of 0.02 mg/kg-day** for this chemical (IRIS) based on numerous animal studies. In studies with rats, effects included changes in the blood, kidney damage, and lesions on the testes (IRIS).

Carcinogenicity

EPA has classified butyl benzyl phthalate as a Class C chemical; a possible human carcinogen. There have been no studies done on humans to test for carcinogenicity, this rating is based solely on rat studies which showed a statistically significant increase in tumors in exposed rats (HSDB). IARC states that carcinogenicity of BBP in humans is not classifiable.

23. CADMIUM

Cadmium is a heavy metal that is released through a wide variety of industrial and agricultural activities. The accumulation of cadmium in human and other biological tissue has been evaluated in both epidemiological and toxicological studies. ATSDR (1999c) has determined that exposure conditions of most concern are long-term exposure to elevated levels in the diet.

Pharmacokinetics

Cadmium is not readily absorbed when exposure occurs via ingestion. Absorption may be much higher in iron-deficient individuals. Evaluations of the impact of cadmium complexation indicate that cadmium absorption from food is not dependent upon chemical complexation. Some populations with high dietary cadmium intakes

have elevated blood cadmium levels, which could be due to the particular forms of cadmium in their food (ATSDR 1999c).

Cadmium is not directly metabolized, but absorption appears to involve sequestering by metallothionein, and plasma cadmium is found primarily bound to this protein. This type of binding appears to protect the kidney. It is thought that kidney damage by cadmium occurs primarily due to unbound cadmium (ATSDR 1999c). Once cadmium is absorbed, it is eliminated slowly; the biological half-life has been estimated at 10 to 30 years (FDA 1993).

Acute toxicity

Effects of acute oral exposure to cadmium include gastrointestinal irritation, nausea, vomiting, abdominal pain, cramps, salivation, and diarrhea. Lethal doses in humans caused massive fluid loss, edema, and widespread organ destruction. The ingested doses were 25 and 1,500 mg/kg (ATSDR 1999c; FDA 1993).

Chronic toxicity

Kidney toxicity is the main concern with cadmium exposure, with the critical effect being significant proteinuria (an indicator of kidney toxicity). The **RfD for cadmium in food was calculated to be 0.001 mg/kg-day** (IRIS). The RfD was calculated using a toxicokinetic model to determine the highest level of cadmium in the human renal cortex not associated with significant proteinuria (EPA 2000).

Cadmium causes many other types of toxic effects in addition to kidney toxicity, such as reducing the gastrointestinal uptake of iron, bone disorders, and increased calcium excretion. Some human studies have shown cardiovascular toxicity and elevated blood pressure, but the results are conflicting (ATSDR 1999c). In addition, animal studies indicate that cadmium causes a wide variety of alterations in the function of the immune system.

Carcinogenicity

No animal or human oral exposure studies suggest that cadmium is carcinogenic via the oral exposure route, although cadmium is classified as a probable human carcinogen (B1) by EPA based on inhalation studies in humans (EPA 2000). ATSDR has concluded that there is minimal evidence of an association between cadmium exposure and increased cancer risk in humans but that the statistical power of the studies examined to detect an effect was not high. They determined that neither the human nor the animal studies provided enough evidence to agree on the carcinogenic status of cadmium by the oral route (ATSDR 1999c).

24. CARBAZOLE

In its pure form, carbazole exists as clear or white crystals. Human exposure to carbazole typically occurs through smoking tobacco and inhaling polluted air. Exposure may also occur through drinking water containing traces of carbazole and

eating charbroiled food. Carbazole is released to the atmosphere in emissions from waste incineration, tobacco smoke, aluminum manufacturing, and rubber, petroleum, coal, and wood combustion. Workers may be exposed to carbazole and other anthracene derivatives via inhalation of vapors and dust and through dermal contact. Carbazole is naturally contained in coal, petroleum, and peat; indicating that it will be released to the environment from the incomplete combustion of these materials. If released to the atmosphere, vapor-phase carbazole is rapidly degraded by photochemically produced hydroxyl radicals leading to an estimated half-life of 3 hours (HSDB).

Pharmacokinetics

No human studies have been conducted. In rats and rabbits, carbazole has been shown to break down into 3-hydroxycarbazole (HSDB).

Acute toxicity

Acute health affects of carbazole on humans have not been studied. Animal studies did not show any acute effects (HSDB).

Chronic toxicity

Chronic effects of carbazole have not been determined in humans, but various types of tumors were observed in rats fed carbazole (HSDB).

Carcinogenicity

No epidemiological data relevant to the carcinogenicity of carbazole to humans are readily available. There is some limited evidence in experimental animals supporting the carcinogenicity of carbazole. Overall, IRAC states that carbazole is not classifiable as to its carcinogenicity to humans and is therefore a Group 3 chemical (HSDB). A HEAST **oral cancer slope factor of 0.02 mg/kg-day** is available for carbazole in the EPA Region 9 PRG table (EPA 2004).

25. CHLORDANE

Chlordane is an organochlorine insecticide comprised of the sum of cis- and trans-chlordane and trans-nonachlor and oxychlordane for purposes of health advisory development. First introduced in 1947, it was used extensively on agricultural crops, livestock, lawns, and for termite control. Because of concern over cancer risk, human exposure, and effects on wildlife, most uses were banned in 1978, and all uses were banned by 1988. Due to its long half-life and ability to concentrate in biological materials, it is still widely distributed in fish in the United States (EPA 2000).

Pharmacokinetics

Chlordane is extremely lipid soluble, and lipid partitioning of chlordane and its metabolites has been documented in both humans and animals. Chlordane is

metabolized via oxidation, which results in a number of metabolites that are very persistent in body fat. Human studies have found chlordane in pesticide applicators, residents of homes treated for termites, and those with no known exposures other than background (EPA 2000).

Acute toxicity

Chlordane is moderately to highly toxic with an estimated lethal dose to humans of 6 to 60 g (IRIS). Effects reported in humans after acute exposure include headaches, irritability, excitability, confusion, loss of coordination, seizures, and convulsions. There is also some evidence that acute exposures to chlordane may be associated with impaired immune function and aplastic anemia in humans (EPA 2000).

Chronic toxicity

IRIS provides an **RfD of 0.0005 mg/kg-day** based on a NOAEL of 0.15 mg/kg-day for hepatic necrosis in a 2-yr feeding study in mice (IRIS). The LOAEL in the principal study was 0.75 mg/kg-day.

Carcinogenicity

Chlordane is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. An increased incidence of hepatocellular carcinoma was observed in both sexes in mice in two separate studies using different strains. Hepatocellular carcinomas were also observed in another study in male mice using a third strain. The **oral cancer slope factor of 0.35 per mg/kg-day** is the geometric mean of the cancer potencies calculated from five data sets (IRIS).

26. CHROMIUM

Trivalent chromium is a naturally occurring chemical with low toxicity. Hexavalent chromium, however, is released into the environment through industrial emissions and is highly toxic due to its strong oxidation characteristics and membrane permeability. Hexavalent chromium is used in chromate manufacturing, ferrochromium industries, and in metal alloys (HSDB).

Pharmacokinetics

Trivalent chromium is an essential ion required for lipid, protein, and fat metabolism and to maintain normal glucose metabolism. The most common routes of exposure to toxic levels of chromium are through inhalation and ingestion (ToxFAQs).

Acute toxicity

The acute toxic effects of hexavalent chromium were studied in 1965 when 155 people were exposed to 20 mg/L hexavalent chromium in their drinking water. The victims suffered from mouth sores, diarrhea, stomachaches, indigestion, vomiting, increased white blood cell counts, and a higher per capita cancer rate. Acute exposure to

hexavalent chromium may also affect fetal development. Dermal exposure to hexavalent chromium can cause skin irritation and allergic contact dermatitis (IRIS).

Chronic toxicity

Chronic exposure to chromium can cause damage to the liver, kidney, and circulatory system, as well as cause nerve tissue damage and dermatitis (OGWDW). **EPA has developed RfDs of 1.5 and 0.003 mg/kg-day for trivalent and hexavalent chromium, respectively** (IRIS). The RfD for hexavalent chromium will be applied to all chromium data in this HHRA since the proportion of trivalent chromium in the total chromium measurements is not known.

Carcinogenicity

EPA has classified trivalent chromium as Group D, not classifiable as to human carcinogenicity. Hexavalent chromium is a Group A known human carcinogen via the inhalation pathway (IRIS). EPA has not developed an oral cancer potency factor for hexavalent chromium.

27. COPPER

Copper occurs naturally in elemental form and as a component of many minerals. Because of its high electrical and thermal conductivity, it is widely used in the manufacture of electrical equipment. Common copper salts, such as the sulfate, carbonate, cyanide, oxide, and sulfide are used as fungicides, as components of ceramics and pyrotechnics, for electroplating, and for numerous other industrial applications (Faust 1992). Copper can be absorbed by the oral, inhalation, and dermal routes of exposure.

Pharmacokinetics

Copper is an essential nutrient that is normally present in a wide variety of human tissues (Faust 1992). Copper is incorporated into more than a dozen specific copper proteins. Copper is essential for hemoglobin formation, carbohydrate metabolism, catecholamine biosynthesis, and cross-linking of collagen, elastin, and hair keratin (EPA 1987).

Acute toxicity

In humans, ingestion of gram quantities of copper salts may cause gastrointestinal, hepatic, and renal effects with symptoms such as severe abdominal pain, vomiting, diarrhea, hemolysis, hepatic necrosis, hematuria, proteinuria, hypotension, tachycardia, convulsions, coma, and death (Faust 1992). Acute inhalation exposure to copper dust or fumes at concentrations of 0.075 to 0.12 mg Cu/m^3 may cause metal fume fever with symptoms such as cough, chills, and muscle ache (Faust 1992). Among the reported effects in workers exposed to copper dust are gastrointestinal disturbances, headache, vertigo, drowsiness, and increase in liver size.

Chronic toxicity

Gastrointestinal disturbances and liver toxicity have resulted from long-term exposure to drinking water containing 2.2 to 7.8 mg Cu/L (Faust 1992). The chronic toxicity of copper has been characterized in patients with Wilson's disease, a genetic disorder causing copper accumulation in tissues. Vineyard workers chronically exposed to Bordeaux mixture (copper sulfate and lime) exhibit degenerative changes of the lungs and liver. Dermal exposure to copper may cause contact dermatitis in some individuals (ATSDR 2004). Additionally, high levels of copper are known to cause kidney and liver damage (ATSDR 2004).

EPA has not developed an oral RfD for elemental copper. EPA's HEAST proposed a provisional value of **0.04 mg/kg-day** (EPA 2005). Provisional RfDs have greater uncertainty than RfDs certified by EPA.

Carcinogenicity

No suitable bioassays or epidemiological studies are available to assess the carcinogenicity of copper (Faust 1992). EPA has placed copper in weight-of-evidence group D, not classifiable as to human carcinogenicity.

28. DDT AND METABOLITES

DDT is an organochlorine pesticide that has not been marketed in the United States since 1972 but is ubiquitous due to its widespread use in previous decades and its relatively long half-life. DDT's close structural analogs, DDE and DDD, are metabolites of DDT and have also been formulated as pesticides in the past (EPA 2000). DDT is very widely distributed; it has been found in wildlife all over the world and in many human samples as well.

Although some use of DDT continues throughout the tropics, it remains of human health concern in the United States primarily due to its presence in water, soil, and food. Because individuals are typically exposed to a mixture of DDE, DDT, and DDD and their degradation and metabolic products, the sum of the 4,4' and 2,4' isomers of DDT, DDE, and DDD will be evaluated together in this HHRA.

Pharmacokinetics

DDT and its analogs are stored in fat, liver, kidney, and brain tissue; trace amounts can be found in all tissues (EPA 2000). DDE is stored more readily than DDT. DDT is eliminated through first-order reduction to DDD and, to a lesser extent, to DDE. The DDD is converted to more water-soluble bis(p-chlorophenyl)acetic acid, with a biological half-life of 1 year. DDE is eliminated much more slowly, with a biological half-life of 8 years. Because elimination occurs slowly, ongoing exposure may lead to an increase in the body burden over time.

Acute toxicity

The low effect dose for severe effects (acute pulmonary edema) in infants has been reported to be 150 mg/kg. In adults, behavioral effects were noted at 5 to 6 mg/kg and seizures at 16 mg/kg (HSDB). Evidence from acute exposure studies of dogs indicates that DDT may sensitize the myocardium to epinephrine. This was observed for both injected epinephrine and epinephrine released by the adrenal glands during a seizure and resulted in ventricular fibrillation. DDT may concurrently act on the CNS, in a manner similar to that of other halogenated hydrocarbons, to increase the likelihood of fibrillation. Chronic exposure to 10 mg/kg-day did not produce increased incidence of arrhythmias in rats or rabbits (EPA 2000).

DDD is considered less toxic than DDT in animals. Symptoms develop more slowly and have a longer duration with DDD than with DDT exposure. Lethargy is more significant and convulsions are less common than with DDT exposure (HSDB).

Chronic toxicity

Extensive research has been conducted on chronic and sub-chronic exposure effects of DDT in animals and in humans working with DDT. These studies have primarily focused on carcinogenic effects, which are discussed in the following section. Studies have also identified liver damage, and there is limited evidence that DDT may cause an increase in the number of white blood cells and decreased hemoglobin level (EPA 2000). Immunological effects have been associated with exposure to DDT.

IRIS lists an **oral RfD of 0.0005 mg/kg-day** for DDT based on liver effects with a NOAEL of 0.05 mg/kg-day from a 27-week rat feeding study conducted in 1950 (IRIS).

Carcinogenicity

DDE, DDT, and DDD are all considered probable human carcinogens (category B2) based on animal studies, with **oral cancer slope factors of 0.24, 0.34, and 0.34 per mg/kg-day**, respectively (IRIS). Liver tumors were associated with each chemical. The occupational studies of workers exposed to DDT are of insufficient duration to assess carcinogenicity (IRIS). Elevated leukemia incidence, particularly chronic lymphocytic leukemia, was noted in two studies of workers. Lung cancer has also been implicated in one study. Bone marrow cells in experimental animals have also been affected by exposure, including an increase in chromosomal fragments in the cells (HSDB). The **oral cancer slope factor for DDT (0.34) is used for total DDTs in this HHRA**, in accordance with EPA (2000) recommendations.

29. DIELDRIN

Dieldrin is an organochlorine pesticide that was phased out between 1974 and 1987. It continues to be detected nationwide due to its relatively long half-life. Dieldrin is also a product of aldrin metabolism (ATSDR 1999a).

Pharmacokinetics

Dieldrin is absorbed from the gastrointestinal tract and transported through the hepatic portal vein and the lymphatic system. Soon after ingestion, it is found in the liver, blood, stomach, and duodenum. Dieldrin is lipophilic and ultimately stored primarily in fat and tissues with lipid components. A correlation between exposure and dieldrin levels in human breast milk has been established, and placental transfer of dieldrin has been observed in women (ATSDR 1999a).

Acute toxicity

The following symptoms are commonly associated with exposure to organochlorines: behavioral changes, sensory and equilibrium disturbances, involuntary muscle activity, depression of vital centers, myocardial irritability, convulsion, and unconsciousness (EPA 2000). Additional effects of dieldrin exposure include: possible hematological effects in humans (ATSDR 1999a). The estimated human lethal dose is 65 mg/kg-day (EPA 2000).

Chronic toxicity

Liver toxicity has been observed in multiple animal studies and in human acute exposure episodes. Neurotoxicity has been observed in humans with chronic inhalation and dermal exposures (ATSDR 1999a). Chronic exposures of pesticide applicators to dieldrin led to idiopathic epilepsy, which ceased when exposure was terminated (EPA 2000).

IRIS provides an **RfD of 0.00005 mg/kg-day for dieldrin** based on a NOEL of 0.005 mg/kg-day from a 1969 2-year rat feeding study that found liver lesions.

Carcinogenicity

Dieldrin is classified as a probable human carcinogen (Group B2) by EPA based on oral studies in animals. EPA has developed an **oral cancer slope factor of 16 per mg/kg-day for dieldrin**. ATSDR has concluded, based on studies that have been reviewed, that dieldrin is probably a tumor promoter. Varieties of tumor types have been observed in animal studies including pulmonary, lymphoid, thyroid, and adrenal (ATSDR 1999a). In addition, dieldrin has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells, and it may cause disruption of the endocrine system due to its estrogenic activity (Soto et al. 1994).

30. ENDRIN AND ENDRIN ALDEHYDE

Endrin is a solid, white, nearly odorless substance that was used in the past as a pesticide to control insects, rodents, and birds. Endrin has not been produced or sold for general use in the United States since 1986. Endrin aldehyde is a minor impurity of the pesticide endrin, which is no longer produced. The production and use of endrin may have resulted in endrin aldehyde's release to the environment through direct release or from various waste streams. Little is known about the properties of endrin

aldehyde (an impurity and breakdown product of endrin) or endrin ketone (a product of endrin when it is exposed to light) (ToxFAQs).

Pharmacokinetics

Endrin can be absorbed by any route. Endrin is metabolized relatively rapidly by the body. Following absorption, the primary target of action is the central nervous system (CNS). Both endrin and its water-soluble metabolites are excreted in urine and feces. Small amounts of the chemical may remain in the fatty tissues of the body (HSDB).

Acute Toxicity

Following exposure to endrin, CNS excitation and convulsions may occur. Respiratory depression may occur concurrently with convulsions, and respiratory failure is the most common cause of death from endrin poisoning. Symptoms in less-severe cases of endrin poisoning may include headache, dizziness, leg weakness, abdominal discomfort, nausea, vomiting, insomnia, agitation, and, occasionally, slight mental confusion. Buildup of fluid in the lungs and kidney damage has been reported following endrin ingestion. Symptoms including headache, dizziness, weakness, lethargy, and weight loss may persist for 2 to 4 weeks (HSDB).

Chronic Toxicity

Enlargement of the liver commonly occurs. Liver enzymes have been induced with occupational exposure. Anorexia, fatigue, and malaise have occurred with chronic exposure to organochlorine insecticides (HSDB). EPA has developed an **RfD of 0.0003 mg/kg-day for endrin** based on animal studies (IRIS).

Carcinogenicity

IARC has assigned a Classification D (not classifiable as to carcinogenicity in humans) for endrin. Animal studies failed to conclusively show carcinogenic effects, and inadequate human exposure data exists to determine carcinogenicity of this compound. Because so little is known about endrin aldehyde, it has been grouped with other organochlorine pesticides and may be assumed to be a class B2 carcinogen (IARC) and therefore a possible human carcinogen. However, there is limited animal evidence and no human studies to support this classification (HSDB and ToxFAQs).

31. GAMMA-BHC (LINDANE) AND METABOLITES (ALPHA-BHC AND BETA-BHC)

Lindane is an organochlorine pesticide that is comprised of isomers of hexachlorocyclohexane (BHC), with the gamma isomer constituting the major (> 99%) component. There appears to be some difference in toxicity of the various hexachlorocyclohexane isomers (EPA 2000). Lindane is used primarily for controlling wood-inhabiting beetles and as a seed treatment. Lindane is also used as a prescription pharmaceutical to control head lice and mites (scabies) in humans.

Pharmacokinetics

Lindane is readily absorbed by the gastrointestinal tract following oral exposure. Distribution is primarily to the adipose tissue but also to the brain, kidney, muscle, spleen, adrenal glands, heart, lungs, blood, and other organs. It is excreted primarily through urine as chlorophenols. The epoxide metabolite may be responsible for carcinogenic and mutagenic effects (EPA 2000). Male exposure to lindane through the environment results in accumulation in testes and semen in addition to the tissues listed above (ATSDR 2005c).

Acute toxicity

The estimated human lethal dose is 125 mg/kg (HSDB). Occupational and accidental exposures in humans have resulted in headaches, vertigo, abnormal EEG patterns, seizures, and convulsions. Death has occurred primarily in children.

Chronic toxicity

Liver damage has been observed in many animal studies and appears to be the most sensitive effect (EPA 2000). Immune system effects have been observed in humans exposed via inhalation and in orally dosed animals. A 5-week study in rabbits found immunosuppression at 1 mg/kg-day (ATSDR 2005c). IRIS provides an **RfD for lindane of 0.0003 mg/kg-day** based on a NOAEL of 0.33 mg/kg-day from a sub-chronic rat study that found liver and kidney toxicity at higher doses (IRIS).

NCEA provides RfDs for lindane's related isomers. The **RfD for alpha-BHC is 0.0005 mg/kg-day** and the **RfD for beta-BHC is 0.0002 mg/kg-day** (EPA 2004). Liver effects are a known result of exposure to both alpha-BHC and beta-BHC (ATSDR 2005c).

Most observed effects in humans exposed accidentally to lindane are neurological. Behavioral effects have also been noted in many studies on experimental animals, and at relatively high levels seizures were reported. More subtle behavioral effects were noted at an LOAEL of 2.5 mg/kg-day with 40 days of exposure in rats. No NOAEL was reported (ATSDR 2005c).

Carcinogenicity

Lindane has been classified as Group B2 (probable human carcinogen) (EPA 2000) and a HEAST **oral cancer slope factor of 1.3 per mg/kg-day** has been listed (EPA 2005). Lindane's related isomers, alpha and beta hexachlorocyclohexane, are classified as probable human carcinogens and have cancer potencies similar to that of lindane: **6.3 per mg/kg-day for alpha-BHC and 1.8 per mg/kg-day for beta-BHC** (IRIS). In addition to tumors identified in experimental animals, human study data indicate that this chemical may cause aplastic anemia (EPA 2000).

32. HEPTACHLOR

Heptachlor is a synthetic chemical that was used in the past for killing insects in homes, buildings, and on food crops. Heptachlor is both a breakdown product and a component of the pesticide chlordane (approximately 10% by weight). Pure heptachlor is a white powder. Technical-grade heptachlor is a tan powder. Heptachlor may be found in the soil or air of homes treated for termites, dissolved in surface water or groundwater, or in the air near hazardous waste sites. Heptachlor is still approved by EPA for killing fire ants in power transformers.

Pharmacokinetics

Approximately 20% of heptachlor is changed within hours into heptachlor epoxide in the environment and in your body. Heptachlor has been shown to bioaccumulate in fish and cattle. People store heptachlor epoxide in their fatty tissue. Some studies show that heptachlor epoxide can still be measured in fatty tissue 3 years after a person is exposed (ToxFAQs). Most of the heptachlor that is swallowed is absorbed into blood. Heptachlor can pass directly from a mother's blood to an unborn baby through the placenta.

Acute toxicity

Blood tests suggest that heptachlor may cause mild liver changes in humans. A few human cases show that breathing pesticide mixtures containing heptachlor may affect the nervous system causing dizziness, fainting, or convulsions (ToxFAQs). Studies of people who made or used pesticides that included heptachlor found no serious health effects. Acute toxicity studies with animals indicate that heptachlor can cause tremors, convulsions, and loss of kidney function at high doses.

Chronic toxicity

Sub-chronic dietary studies with mice resulted in liver and adrenal gland damage. Animals that ate food containing heptachlor before and/or during pregnancy had smaller litters (ToxFAQs). EPA has established an **RfD of 0.0005 mg/kg-day** for heptachlor based on a 2-yr rat feeding study that documented increased liver weight in males (IRIS).

Carcinogenicity

Animals fed heptachlor throughout their lifetime had more liver tumors than animals that ate food without heptachlor. EPA has classified heptachlor as a probable human carcinogen (B2) and established an **oral cancer slope factor of 4.5 per mg/kg-day** (IRIS).

33. HEPTACHLOR EPOXIDE

Heptachlor epoxide is a breakdown product of the organochlorine pesticides heptachlor and chlordane and is a contaminant of both products. It is more toxic than

either parent compound (ATSDR 2005b). Although most uses of heptachlor were suspended in 1978 and chlordane was removed from the market in 1988 (EPA 2000), heptachlor epoxide continues to be a widespread contaminant due to its relatively long half-life.

Pharmacokinetics

Based upon animal and limited human data, heptachlor epoxide is absorbed through the gastrointestinal tract and is found primarily in the liver, bone marrow, brain, and fat, although it is distributed widely to other tissues as well. It is stored primarily in fat. Fetal blood levels were approximately four times those measured in women.

Heptachlor epoxide has a very long half-life, particularly in adipose tissue. Human tissue levels have correlated well to age, with 97 percent of North Texas residents tested (ages 41 to 60) having measurable levels. Based on the Texas study, heptachlor epoxide tissue levels have not decreased appreciably since the 1960s (EPA 2000).

Acute toxicity

The LD50s for heptachlor epoxide range from 40 to 162 mg/kg in rodents (EPA 2000).

Chronic toxicity

IRIS provides an **RfD of 0.000013 mg/kg-day** based on an LOAEL of 0.0125 mg/kg-day from a 60-week dog feeding study reported in 1958. The critical effect was increased liver-to-body-weight ratios in both males and females at the lowest dose tested.

Animal studies have identified the following effects associated with heptachlor (and subsequently heptachlor epoxide via metabolism) or heptachlor epoxide directly: elevated bilirubin and white blood cell count, increased serum creatinine phosphokinase levels suggestive of muscle damage, muscle spasms secondary to CNS stimulation, adrenal gland pathology, and neurological disorders (EPA 2000).

Carcinogenicity

Heptachlor epoxide is classified as a probable human carcinogen (category B2) by EPA based on oral studies in animals. The **oral cancer slope factor is 9.1 per mg/kg-day** (IRIS). This value is based on the geometric mean of several studies that identified liver carcinomas.

Heptachlor (and consequently heptachlor epoxide) exposures have been associated with brain tumors in children exposed prenatally. Multiple chromosomal abnormalities were also identified in the tumor cells. It was not determined whether the effects were caused by environmental or familial factors (EPA 2000).

34. HEXACHLOROBENZENE

Hexachlorobenzene is a byproduct of manufacturing and in the past it has been used as a fungicide seed protectant. At ambient temperatures, it exists as a solid, and in aquatic environments, it is found in higher quantities in sediment than water due to its low solubility (ATSDR 2002).

Pharmacokinetics

Hexachlorobenzene is persistent in the body due to its lipophilic nature. It is found in human breast milk (ATSDR 2002), which may be a significant route of exposure for young children.

Acute toxicity

The following symptoms are commonly associated with exposure to organochlorines: behavioral changes, sensory and equilibrium disturbances, involuntary muscle activity, depression of vital centers, myocardial irritability, convulsion, and unconsciousness (EPA 2000). Acute exposure studies in animals have demonstrated a low acute toxicity for hexachlorobenzene with LD50s between 1,700 and 4,000 mg/kg. Based on animal studies, the following systems are negatively affected following acute exposure: liver, kidney, hematological, and dermal (ATSDR 2002).

Chronic toxicity

A large number of people in Turkey were exposed from 1955 to 1959 to grain contaminated with hexachlorobenzene. Precise exposure estimates are not available, but it was estimated that exposure levels of 0.7 to 2.9 mg/kg-day for a 70-kg individual occurred (ATSDR 2002). The following effects were associated with this exposure: shortening of the digits due to osteoporosis, painless arthritis, muscle weakness, rigidity and sensory shading, thyroid enlargement, and histopathological changes in the liver often accompanied by skin lesions (ATSDR 2002). These effects have also been observed in numerous animal studies.

Based on animal studies, the hepatic system appears to be the most sensitive systemic endpoint for hexachlorobenzene exposure. The results from these studies have been converted by EPA to an **RfD of 0.0008 mg/kg-day** in the IRIS database.

Carcinogenicity

Carcinogenic assays of hexachlorobenzene in animals have identified an increased incidence of multiple tumor types. Hexachlorobenzene is classified as a possible human carcinogen (B2) based on the results of animal studies (EPA 2000). EPA has established an **oral cancer slope factor of 1.6 per mg/kg-day** (IRIS). Follow-up studies of the exposure of hexachlorobenzene to the victims in Turkey have not identified cancers in the 25-year or 20- to 30-year exposure cohorts. However, ATSDR notes that the enlarged thyroids noted in members of these cohorts have not been adequately investigated (ATSDR 2002).

35. HEXACHLOROBUTADIENE

Hexachlorobutadiene, also known as HCBD, is formed during the processing of other chemicals such as tetrachloroethylene, trichloroethylene, and carbon tetrachloride. Hexachlorobutadiene is an intermediate in the manufacture of rubber compounds and lubricants. It is used as a fluid for gyroscopes, a heat transfer liquid, or a hydraulic fluid. Outside of the United States it is used to kill soil pests (ToxFAQs).

Pharmacokinetics

In animal studies, most of the hexachlorobutadiene is metabolized into more toxic compounds. It is not known how rapidly hexachlorobutadiene and its breakdown products are removed from your body through your urine and feces. Some is expected to remain in your body fat for long periods (ToxFAQs).

Acute toxicity

Ingestion of hexachlorobutadiene damaged the kidneys of rats and mice and, to a lesser extent, the liver of rats. These effects occurred after both short- and long-term exposures at very low dose levels. Young rats were affected more than adult rats. The kidneys of female rats appeared to be affected more than those of males. On the other hand, the liver of male rats was affected, but the liver of female rats was not. It is not clear if the differences between the sexes might be seen in humans. Kidney, brain, and liver damage were also seen in rabbits after contact of their skin with the compound for a short period.

Chronic toxicity

Hexachlorobutadiene was shown to affect the function of the liver in one study of workers at a solvent production plant who breathed hexachlorobutadiene for long periods. Hexachlorobutadiene decreased fetal body weight in rats, but did not affect fetal development or impair their ability to produce offspring. The lungs, heart, brain, blood, muscles, and skeleton in rats or mice were not damaged after long-term exposure. HEAST developed an **RfD of 0.0002 mg/kg-day for hexachlorobutadiene** (EPA 2005).

Carcinogenicity

Studies in rats indicate that hexachlorobutadiene may increase the risk of kidney cancer if exposures occur for long periods. EPA has classified hexachlorobutadiene as a possible human carcinogen (C) based on observations of renal neoplasms in male and female rats in one study. EPA established an **oral cancer slope factor of 0.078 per mg/kg-day** (IRIS).

36. HEXACHLOROCYCLOPENTADIENE (HCCPD)

HCCPD is a manufactured chemical that does not exist naturally in the environment. It is a light, lemon-yellow liquid with a sharp musty odor. It easily evaporates into the

air where the vapor looks like a blue haze. HCCPD is a component used in the manufacture of certain pesticides. In addition to the use as a pesticide, it is also used to make flame retardants, resins that won't burn, shock-proof plastics, esters, ketones, fluorocarbons, and dyes. HCCPD most commonly enters the environment during its production and disposal. When HCCPD becomes airborne, it is broken down quickly by sunlight and reactions with other chemicals. HCCPD doesn't dissolve readily in water, and will evaporate from the surface. About half the HCCPD in water will be changed to other chemicals by light in only 4 minutes. HCCPD that gets into soil binds to decaying plant and animal matter. If the soil is sandy, HCCPD can move through it to reach underground water. About half of the HCCPD in the soil will be changed to other chemicals by bacteria in 1 to 2 weeks. Small amounts of HCCPD can accumulate in fish (ToxFAQs).

Pharmacokinetics

HCCPD primarily targets the tissues that line the lungs, regardless of the exposure route. Cough, dyspnea, and chest discomfort have been reported in exposed humans. Experimental animals have developed pulmonary edema, pulmonary hemorrhages, and necrotizing bronchitis and bronchiolitis.

Acute Toxicity

HCCPD is highly irritating and corrosive to tissues. Exposure effects may include cough, dyspnea, chest discomfort, headache, dizziness and burns. Proteinuria and elevated levels of liver enzymes may occur. Pulmonary damage may range from bronchitis, chemical pneumonitis, bronchiolitis, and pulmonary edema to respiratory failure. Degenerative changes of the brain, heart, liver (elevations in liver enzymes), adrenals, and kidneys have been reported (HSDB).

Chronic Toxicity

Long term exposure has not been studied in humans. However, sub-chronic or pre-chronic exposure to HCCPD vapors caused lacrimation, salivation, gasping, and at high concentrations, tremors in laboratory animals. Diffuse degenerative changes were observed in the brain, heart, liver, adrenal glands, and kidneys. Severe pulmonary edema and acute necrotizing bronchitis and bronchiolitis demonstrated the severity of irritation with incidence and severity dependent on dose. During testing on animal models, adverse effects were observed at the lowest exposure concentration (0.15 ppm) (HSDB). Due to the lack of available human data, EPA has developed an **RfD of 0.006 mg/kg-day** for HCCPD based on animal studies (IRIS).

Carcinogenicity

IARC has given HCCPD a classification D status, meaning that it is not classifiable as to human carcinogenicity. This ruling is based on inadequate data in humans and animals concerning carcinogenicity of HCCPD (HSDB and ToxFAQs).

37. HEXACHLOROETHANE

Hexachloroethane is a colorless solid that gradually evaporates when it is exposed to air. It is also called HCE, perchloroethane, and carbon hexachloride. Its vapors smell like camphor. In the United States, about half of the hexachloroethane is used by the military for smoke-producing devices. It is also used to remove air bubbles in melted aluminum. Hexachloroethane may be present as an ingredient in some fungicides, insecticides, lubricants, and plastics. Hexachloroethane does not occur naturally in the environment. It is no longer made in the United States, but it is formed as a byproduct in the production of some chemicals. Some hexachloroethane can be formed by incinerators when materials containing chlorinated hydrocarbons are burned. Hexachloroethane itself does not catch fire easily. Some hexachloroethane can also be formed when chlorine reacts with carbon compounds in drinking water. Hexachloroethane can be released to the environment during its production, use, transport, or disposal. In air, hexachloroethane does not break down to other compounds. Some hexachloroethane that is in lakes or streams and surface soils will evaporate into the air. Microscopic organisms can break it down more easily in an anaerobic environment (without oxygen) than with oxygen. Hexachloroethane does not appear to build up in plants or animals used for food (ToxFAQs).

Pharmacokinetics

Following absorption, hexacloroethane is distributed systemically, but tends to accumulate in fat. Metabolism of hexachloroethane in animals has been shown to be rather extensive. Multiple chlorine atoms are removed by the cytochrome P450 complex, and the resulting metabolites, primarily trichloroethanol or trichloroacetic acid, have been shown to be excreted in urine. The half life in mice is thought to be 2.5 days (HSDB).

Acute Toxicity

Exposure has caused eye irritation, lacrimation and redness, but no lasting damage. Hexachloroethane is also irritating to the skin and may act as a central nervous system depressant (HSDB).

Chronic Toxicity

Hexachloroethane is not a very toxic substance. Significant exposure over a long period of time may cause damage to the liver and kidneys. Animal studies have not shown hexachloroethane to cause birth defects or to affect reproduction (ToxFAQs). EPA has developed an **RfD of 0.001 mg/kg-day** for HCCPD based on animal studies (IRIS).

Carcinogenicity

There is inadequate evidence in humans for the carcinogenicity of hexachloroethane. Because there is sufficient evidence in experimental animals for the carcinogenicity of

hexachloroethane, IARC has given it a classification of group 2B, and considers it to be a possible carcinogen to humans (HSDB). EPA developed an **oral cancer slope factor of 0.014 per mg/kg-day** for hexachloroethane, and ranks the chemical in group C, a possible human carcinogen because cancer was observed in one strain of mice following exposure to hexachloroethane (IRIS).

38. IRON

Iron is the second most abundant metal in the earth's crust. The most common iron ores include hematite, magnetite, limonite, and siderite (HSDB). Iron salts are used as fertilizer micronutrients, herbicides, electrolytes in dry cell batteries, animal feed additives, galvanizers, and as emulsion breakers. The major route of exposure to iron is through the mining and handling of iron ores (HSDB).

Pharmacokinetics

Iron is found naturally in the body as an important component of hemoglobin. In overdoses (>20 mg/kg-day), iron may be absorbed into the body may be extremely fast, where it is incorporated into structural proteins (Spanierman 2001). Excretion may be extremely slow in these cases.

Acute toxicity

Acute iron toxicity is the main cause of pediatric poisoning death in the United States. The hallmark feature of iron overdose is gastrointestinal bleeding. Iron is an extremely corrosive substance in the gastrointestinal tract. The absorption of excessive quantities of ingested iron will result in systemic iron toxicity. Severe overdose causes impaired mitochondrial dysfunction, which can result in cellular death. One of the most affected organs is the liver, but other organs, such as the heart, kidneys, lungs and the hematologic systems may be impaired (Spanierman 2001).

Chronic toxicity

Chronic exposure to iron oxide fume or dust can cause the appearance of a pulmonary condition called siderosis. This is considered a benign condition and does not ordinarily cause significant physiologic impairments (HSDB). Iron is also suspected to be a cardiovascular or blood toxicant, gastrointestinal or liver toxicant, neurotoxicant, and respiratory toxicant (HSDB). EPA's NCEA has developed a **provisional RfD for iron of 0.3 mg/kg-day** (EPA 2005). Provisional RfDs have greater uncertainty than RfDs published by EPA in the IRIS database.

Carcinogenicity

At this time, there is no information regarding the carcinogenicity of iron to humans or animals.

39. LEAD

Lead is a naturally occurring bluish-gray metal found in small amounts in the earth's crust. Lead's most important industrial use is in the production of some types of batteries. It is also used in the production of ammunition, in some kinds of metal products (such as sheet lead, solder, some brass and bronze products, and pipes), and in ceramic glazes. Human activities (such as the former use of "leaded" gasoline) have spread lead and substances that contain lead to all parts of the environment. Before the use of leaded gasoline was banned, most of the lead released into the US environment came from car exhaust. Other sources of lead released to the air include burning fuel, such as coal or oil, industrial processes, and burning solid waste.

Sources of lead in dust and soil include lead that falls to the ground from the air, and weathering and chipping of lead-based paint from buildings and other structures. Lead in dust may also come from windblown soil. Disposal of lead in municipal and hazardous waste dump sites may also add lead to soil. Mining wastes that have been used for sandlots, driveways, and roadbeds can also be sources of lead (ATSDR 1999d).

People living near hazardous waste sites may be exposed to lead and chemicals that contain lead by breathing air, drinking water, eating foods, or swallowing or touching dust or dirt that contains lead. For people who do not live near hazardous waste sites, exposure to lead may occur in several ways: 1) by eating foods or drinking water that contain lead, 2) by spending time in areas where leaded paints have been used and are deteriorating, 3) by working in jobs where lead is used, 4) by using health-care products or folk remedies that contain lead, and 5) by having hobbies in which lead may be used such as sculpturing (lead solder) and staining glass.

Pharmacokinetics

Absorbed lead is distributed in various tissue compartments.

Acute toxicity

Lead can affect almost every organ and system in your body. The most sensitive is the central nervous system, particularly in children. Studies have shown that children exposed to low levels of lead have lower IQs, reduced motor skills, developmental problems, hyperactivity, and increased aggression (Canfield et al. 2003; Pattee and Pain 2003).

Lead also damages kidneys and the reproductive system. The toxic effects of lead are the same regardless of the route of entry into the body, and they are correlated with internal exposure as blood lead level.

Chronic toxicity

At high levels over long periods of time, lead may decrease reaction time, cause weakness in fingers, wrists, or ankles, and possibly affect the memory. Lead may

cause anemia, a disorder of the blood. It can also damage the male reproductive system. Even low levels of exposure to lead may have significant effects.

Since most of the toxicity data for lead is based on an internal dose, a reference dose, which is based on an external dose (i.e., mg/kg-day) has not been developed. Data on external exposure (i.e., mg/kg-day) are available from animal studies, but these data are generally not used to assess human health impacts because of the large database available using blood levels. Risks from lead exposure were evaluated using the IEUBK model for young children and the adult lead model for risks to fetal development, as described in Section B.3.4.4. EPA and the Centers for Disease Control and Prevention have determined that child or fetal blood lead concentrations at or above 10 µg/dL present risks to children's health.

Carcinogenicity

The Department of Health and Human Services has determined that lead acetate and lead phosphate may reasonably be anticipated to be carcinogens based on studies in animals. There is inadequate information to clearly determine lead's carcinogenicity in people (ToxFAQs).

40. MANGANESE

Manganese is an element considered essential to human health. However, divalent manganese is about 2.5 to 3 times more toxic than trivalent manganese, and the anions of manganese salts influence the overall manganese toxicity. Industrial activities which use manganese include steel manufacturing, nonferrous alloys, purifying and scavenging agent in metal production, manufacturing of aluminum, ceramics, matches, glass, and welding rods (HSDB).

Pharmacokinetics

Humans ingest manganese from three main sources: diet, drinking water, and inhaled particles. Manganese that is inhaled is mostly brought up from the respiratory tract by ciliary action and swallowed, eventually being absorbed in the gastrointestinal tract (Clayton and Clayton 1981). After oral exposure, absorbed manganese is quickly eliminated from blood and distributed mainly to the liver, kidneys, and endocrine glands. Minor amounts go to the brain and bone as shown in studies using mice, rats and monkeys.

Acute toxicity

Acute manganese poisoning has effects similar to other heavy metals if dust or fumes are inhaled in sufficient quantity. The minimum dose that produces effects on the central nervous system is not known and, with few exceptions, such effects have been observed only in occupationally exposed individuals. Sixteen cases of manganese poisoning have been described for a small Japanese community, three of which were fatal (including one suicide). The manganese content of the water was about 14 mg/L

and concentrations of about 8 and 11 mg/L were found in two other wells. The subjects exhibited psychological and neurological disorders associated with manganese poisoning and high manganese and zinc levels were found in organs at autopsy (WHO 1981).

Chronic toxicity

The usual form of chronic manganese poisoning primarily involves the central nervous system. Early symptoms include, languor, sleepiness, and weakness in legs, emotional disturbances such as uncontrollable laughter and a tendency to fall while walking (ACGIH 1986). Long-term exposure to manganese is known to cause a condition with symptoms that are similar to Parkinson's disease and are debilitating and permanent. Exposure to this metal has also been linked to reproductive problems and reduced red and white blood cell counts (ATSDR 2000a).

Experimental studies have suggested that populations at greatest risk of adverse effects due to manganese exposure are the very young and those with an iron deficiency, and workers exposed to manganese at or near the recommended threshold limit value. EPA has established an **RfD of 0.14 mg/kg-day** for a 70 kg adult (IRIS).

Carcinogenicity

Manganese is not classified as a carcinogen to humans (a class D chemical) because existing studies are inadequate to assess the carcinogenicity of manganese to humans and animals (ToxFAQs).

41. MERCURY

Mercury is widely distributed in the environment due to both natural and anthropogenic processes. It is released generally as elemental mercury (Hg^0) or divalent mercury (Hg^{2+}). It can be converted between these forms and may form mercury compounds by chemical processes in air, water, and soil. Biological processes in other media, primarily soil and sediment, can convert inorganic mercury into organic mercury, primarily methylmercury. In fish tissue, the majority of mercury is in the form of methylmercury (EPA 2000).

Pharmacokinetics

Methylmercury is rapidly and nearly completely absorbed; estimates of absorption efficiency are 90 percent or greater (ATSDR 1999e; EPA 1997c; WHO 1990). Methylmercury is readily distributed to all tissues following absorption from the gastrointestinal tract. Methylmercury in the body is considered to be relatively stable and is only slowly demethylated to form mercuric mercury. Estimates for the half-life of methylmercury in the body range from 44 to 80 days (EPA 1997c).

Methylmercury binds readily to protein and can be found throughout fish tissue. A substantial portion of the mercury in fish can be found in trimmed filets, making it difficult to reduce exposure by trimming fat and skin prior to cooking (EPA 2000).

Acute toxicity

Acute high-level exposures to methylmercury may result in kidney damage and failure, gastrointestinal damage, cardiovascular collapse, shock, and death. The estimated lethal dose is 10 to 60 mg/kg-day (ATSDR 1999e).

Chronic toxicity

Neurotoxicity is the chronic effect of greatest concern, both to the developing embryo or fetus and to adults and children (EPA 2000). Neurotoxicological effects include tremors, decreased IQ, and decreased motor function. In addition, damage to the liver and kidney can occur with chronic exposure (ATSDR 1999e). Effects to humans from consumption of contaminated food have been documented in Japan and Iraq.

The current IRIS **RfD for methylmercury of 0.0001 mg/kg-day** was originally based on data on neurological changes in 81 Iraqi children who had been exposed *in utero*. This value was subsequently updated using data from a population in the Faroe Islands who were exposed to methylmercury and PCBs through consumption of fish and pilot whale. In deriving the RfD, EPA used a benchmark dose (BMD) approach to quantify a dose-effect relationship between methylmercury in cord blood and a neurological endpoint. A BMD limit of 58 µg/L cord blood was estimated based on findings from the Boston Naming Test, a neuropsychological evaluation. A methylmercury intake level associated with a blood level of 58 µg/L was then calculated to be 1.0 µg/kg-day. The current RfD of 0.1 µg/kg-day (i.e., 0.0001 mg/kg-day) derived from the Faroe Islands data, is thus unchanged from the previous RfD derived from the Iraqi data. The RfD for methylmercury is used for mercury in this HHRA.

Carcinogenicity

Methylmercury is currently a Class C chemical, a possible carcinogen based on inadequate data in humans and limited evidence in animals. Dietary exposure of mice to methylmercury resulted in significant increases in the incidences of kidney tumors in males but not in females (EPA 1997c). Evidence points to a mode of action for methylmercury carcinogenicity that operates at high doses certain to produce other types of toxicity in humans. Given the relatively low levels of exposure, even among consumers of highly contaminated fish, methylmercury is not likely to present a carcinogenic risk to the US population (EPA 2000). An oral slope factor is currently not available for methylmercury.

42. MOLYBDENUM

Molybdenum occurs as a dark-gray or black powder with metallic luster or as a mass of silver-white color. In nature, molybdenum occurs in small amounts in the earth's crust (HSDB). Common industrial activities in which exposure to soluble molybdenum compounds may occur include molybdenum steel processing, welding operations, petroleum refining, manufacture of corrosion inhibitors, application of agricultural chemicals, and electroplating processes (HSDB).

Pharmacokinetics

While the mechanism of molybdenum toxicity is not yet fully understood, it is assumed that the primary factor is the formation of a copper-containing complex in the gastrointestinal tract which reduces the body's ability to utilize copper. Molybdenum has been found to accumulate in large amounts in the liver, and another study found a high accumulation in the lungs, spleen, and heart of rats exposed to chronic inhalation. In the blood stream, molybdenum binds to red blood cells and plasma proteins. Molybdenum is excreted rapidly as a molybdate, and excesses may also be excreted by the bile (HSDB).

Acute toxicity

Most molybdenum toxicity studies have been conducted over an extended time period, and thus little acute toxicity is available. Due to the relatively lower toxicity of molybdenum as compared to most metals, a massive dose would be required to cause harmful effects in humans (IMOA 2006). Exposure to molybdenum has been reported to cause diarrhea in animals such as cows (HSDB).

Chronic toxicity

Chronic exposure of humans to molybdenum may result in increased uric acid levels, gout-like symptoms, and anemia. Animal studies also reported damage to the kidney and liver, as well as impaired reproductive functions and sterility (HSDB). EPA's IRIS has developed an **RfD of 0.005 mg/kg-day** for molybdenum based on elevated uric acid levels in humans who were exposed to the chemical.

Carcinogenicity

No information is available regarding the carcinogenicity of molybdenum to humans or animals (HSDB, IRIS).

43. NICKEL

Nickel is used in a wide variety of industries. Occupational exposure is the predominant cause of harmful exposure to nickel.

Pharmacokinetics

Nickel is toxic to the liver in animals and is shown to affect kidney function in humans. It binds to tissues within the kidney and reduces their ability to function. Divalent nickel ions can penetrate the skin through openings at sweat ducts and hair follicles. The ions then bind with keratin and cause contact dermatitis. Nickel has a biological half-life of 20 to 34 hours in plasma and 17 to 39 hours in urine (HSDB).

Acute toxicity

Dermal contact with nickel causes contact dermatitis. Nickel poisoning occurred in 23 dialyzed patients when nickel leached in dialysate from a nickel-plated stainless steel

water heater. The victims experienced nausea, vomiting, weakness, headache, and palpitation (HSDB).

Chronic toxicity

Nasal and lung cancer have resulted from chronic inhalation of nickel particles (IRIS). Damage to the nasal mucosa, asthma, pneumoconiosis, and conjunctivitis have also been observed after long term exposure (HSDB). EPA has developed an **RfD of 0.02 mg/kg-day for nickel** based on decreased body and organ weights in a long-term rat feeding study (IRIS).

Carcinogenicity

EPA has classified nickel refinery dust as a known (Class A) carcinogen, but the soluble salts of nickel on which the oral RfD is based are not classified as carcinogenic. This classification was based on a study of sulfide nickel matte refinery workers who developed lung and nasal tumors after being exposed to nickel refinery dust, and also on data collected from nickel carcinogenicity studies with rats (IRIS).

44. NITROBENZENE

Nitrobenzene is an industrial chemical. It is an oily yellow liquid with an almond-like odor. It is produced in large quantities for use in industry. Most of the nitrobenzene produced in the United States is used to manufacture a chemical called aniline. Nitrobenzene is also used to produce lubricating oils such as those used in motors and machinery. A small amount of nitrobenzene is used in the manufacture of dyes, drugs, pesticides, and synthetic rubber. Very small amounts of nitrobenzene may be found in the air, and although nitrobenzene dissolves only slightly in water it will evaporate to air. It may be present in water from industrial releases. In water, nitrobenzene will be broken down by sunlight. Nitrobenzene in soil can move into the groundwater, be taken up by plants, evaporate to the air, and be broken down by bacteria. It does not appear to concentrate in fish or other aquatic animals (ToxFAQs).

Pharmacokinetics

Nitrobenzene is metabolized via two main pathways that yield aniline and nitrophenols. All metabolites were observed to be excreted through urine in lab animals with a half life of approximately 2 days (HSDB).

Acute toxicity

Nitrobenzene may be toxic by all routes of exposure, depending on dose; usual routes of exposure are inhalation of vapor and skin contact with vapor or liquid. The mean adult lethal oral dose is estimated to be about 1 to 5 grams. Alcohol ingestion may worsen the effects. Symptoms of exposure may include eye and skin irritation and methemoglobinemia, associated with headache, cyanosis, weakness, dizziness, confusion, rapid heart rate, labored breathing, chest pain, nausea and vomiting, and

coma. These are usually delayed in onset for up to 1 to 4 hours. A bitter almond odor may be present in urine or vomit, which suggests cyanide poisoning, but cyanide produces symptoms much more rapidly than nitrobenzene (HSDB).

Chronic toxicity

Chronic exposure may produce liver toxicity (HSDB). EPA has developed an **RfD of 0.0005 mg/kg-day** for Nitrobenzene based on animal studies (IRIS).

Carcinogenicity

No studies are available on whether nitrobenzene causes cancer in people. In animals, breathing nitrobenzene resulted in an increase in liver, thyroid, and kidney tumors. IARC has determined that nitrobenzene is a group 2B chemical, and is possibly carcinogenic to humans. However, EPA's IRIS states that nitrobenzene is not classifiable as to human carcinogenicity, and is a group D chemical. Both sources state that insufficient evidence exists to fully evaluate the carcinogenicity of this compound (ToxFAQs, IRIS).

45. N-NITROSODIMETHYLAMINE

N-nitrosodimethylamine is not currently used in industrial processes, except for research purposes where it may be released to the environment with laboratory waste. It was once used as an antioxidant, additive for lubricant, as a softener of copolymers, and in the production and use of rocket fuels (HSDB).

Pharmacokinetics

N-nitrosodimethylamine is absorbed from gastrointestinal tract and lung; skin absorption is slow. When administered to rats, mice, and rabbits, it is distributed uniformly in tissue and has a half-life of approximately 4 hr. Although the liver is the main organ concerned with its metabolism and is a site of selective toxicity, N-nitrosodimethylamine does not concentrate there (HSDB).

Acute toxicity

Systemic effects are characterized by onset in a few hours of nausea and vomiting, abdominal cramps and diarrhea. Headache, fever, and weakness may also occur. Ultimately liver disease may result (HSDB).

Chronic toxicity

Chronic toxic effects other than liver disease and cancer have not been well-documented (ToxFAQs). EPA has established a **provisional RfD of 0.000008 mg/kg-day** for N-nitrosodimethylamine (EPA 2004).

Carcinogenicity

EPA has classified N-nitrosodimethylamine as a probable human carcinogen (B2) based on the induction of tumors at multiple sites in both rodents and non-rodent mammals exposed by various routes (IRIS). EPA has established an **oral cancer slope factor of 51 per mg/kg-day** (IRIS).

46. N-NITROSO-DI-N-PROPYLAMINE

N-Nitroso-di-n-propylamine is produced primarily as a research chemical and not for commercial purposes. However it has been identified as a contaminant in the substituted dinitrotrifluralin herbicides, and thus may be released to the environment when these herbicides are used and from spills, as well as from some industrial effluents. The general population may be exposed to N-nitroso-di-n-propylamine in spray drifts from fields where trifluralin is used. N-Nitroso-di-n-propylamine is rarely found in food (HSDB).

Pharmacokinetics

N-Nitroso-di-n-propylamine is distributed evenly throughout the body. When administered to pregnant animals, the compound crosses the placental barrier and can be found in fetal tissue. It has been measured in milk and blood one hour after oral administration (HSDB).

Acute toxicity

Acute toxic effects from N-nitroso-di-n-propylamine are not well-documented.

Chronic toxicity

Chronic toxic effects other than teratogenicity and carcinogenicity have not been well-documented. EPA has not established an RfD for N-nitroso-di-n-propylamine (IRIS).

Carcinogenicity

EPA has classified N-nitroso-di-n-propylamine as a probable human carcinogen (B2) based on the increased tumor incidence at multiple sites in two rodent species and in monkeys administered the compound by various routes. EPA has established an **oral cancer slope factor of 7 per mg/kg-day** (IRIS).

47. N-NITROSODIPHENYLAMINE

N-Nitrosodiphenylamine (NNDP) is an industrial compound. It is an orange-brown or yellow solid that has been produced since 1945 to make rubber products such as tires or to make other chemicals. In the early 1980s, most US rubber manufacturers replaced it with more efficient chemicals, and now, only one manufacturer in the United States produces this chemical. Whether or not it occurs naturally in the environment remains unknown, but there is some evidence that micro-organisms make it (ToxFAQs).

Pharmacokinetics

Evidence in animals has found that NNDP is metabolized to 1,1-diphenylhydrazine in the liver. Additionally, increased levels of nitrate and diphenylamine were detected in the urine of rats given NNDP (HSDB).

Acute toxicity

No acute toxicity information is available for humans. Mortality was observed in two studies in which NNDP was orally administered at high levels to mice and rats (HSDB).

Chronic toxicity

Overall little information regarding the health effects of exposure to NNDP. However, animal studies have identified levels and exposures that can cause death. Animals given high levels of NNDP in their diets for long periods of time developed liver damage, swelling, cancer of the bladder, and changes in body weight (ToxFAQs). A provisional **RfD of 0.02 mg/kg-day** was developed by EPA (2004) for NNDP.

Carcinogenicity

While there is no evidence of carcinogenicity in humans, EPA has characterized NNDP as a probable human carcinogen based on the limited available animal studies. In a long-term study done, rats showed an increase in bladder cancer after being exposed to high levels of NNDP (HSDB). EPA has developed an **oral cancer slope factor of 0.0049 per mg/kg-day** for NNDP (IRIS).

48. PENTACHLOROPHENOL

Pentachlorophenol is a man-made substance that does not occur naturally in the environment. At one time, it was one of the most widely used biocides in the United States. Now the purchase and use of pentachlorophenol are restricted to certified applicators. It is no longer available to the general public. Application of pentachlorophenol in the home as an herbicide and pesticide accounted for only 3% of its consumption. Before use restrictions, pentachlorophenol was widely used as a wood preservative. It is now used industrially as a wood preservative for power line poles, cross arms, and fence posts (ToxFAQs).

Pharmacokinetics

The most common exposure routes for pentachlorophenol are inhalation and dermal contact. Human studies have estimated half lives of less than 33 hours. Bioaccumulation appears to be minor; most absorbed pentachlorophenol does not break down, but instead leaves in urine. Much smaller amounts leave in feces (ToxFAQs).

Acute toxicity

Many, but not all, the harmful effects associated with exposure to pentachlorophenol may be due to impurities present in commercial pentachlorophenol. Short exposures to large amounts of pentachlorophenol in the workplace or through the misuse of products that contain it can cause harmful effects on the liver, kidneys, blood, lungs, nervous system, immune system, and gastrointestinal tract. Contact with pentachlorophenol (particularly in the form of a hot vapor) can irritate the skin, eyes, and mouth. If large enough amounts enter the body, heat is produced causing an increase in body temperature. The body temperature can increase to dangerous levels, causing injury to various organs and tissues and even death (ToxFAQs).

Chronic toxicity

Long-term exposure to low levels such as those that occur in the workplace can cause damage to the liver, kidneys, blood, and nervous system. The major organs or systems affected by long-term exposure to low levels in animals are the liver, kidney, nervous system, and immune system. All these effects get worse as the level of exposure increases (ToxFAQs).

EPA has established an **RfD for pentachlorophenol of 0.03 mg/kg-day** based on a rat chronic oral study that documented liver and kidney pathology (IRIS).

Carcinogenicity

EPA's IRIS database classifies pentachlorophenol as a probable human carcinogen (B2) and provides an **oral cancer slope factor of 0.12 per mg/kg-day** based on statistically significant increases in the incidences of multiple biologically significant tumor types in mice. In addition, a high incidence of two uncommon tumors was also observed.

49. SILVER

Silver is toxic by all routes of exposure. Exposure is predominantly occupational via industries associated with electroplating, photographic materials, brazing, welding, and the manufacturing of jewelry, mirrors, coinage, pigments, and antiseptics (HSDB).

Pharmacokinetics

Silver is retained in all body tissues. It is primarily deposited in the skin, adrenals, lung, muscle, pancreas, kidney, heart, and spleen. Excretion of silver from the body is mainly via the gastrointestinal tract. Silver has a biological half-life of 1.7 to 2.5 days, as determined in studies using dogs, rats, monkeys, and mice (HSDB).

Acute toxicity

Acute exposure to silver can result in skin and eye irritation, mild bronchitis, metal fume fever and hepatic damage, stomach pain, and lung and throat irritation (HSDB).

Chronic toxicity

The most common result of chronic exposure to silver is generalized argyria, a blue-gray discoloration of the skin, mucous membranes, and eyes (HSDB). Workers involved in manufacturing precious metal powder experienced elevated urine and blood silver concentrations and respiratory irritation. EPA has calculated the **RfD for silver at 0.005 mg/kg-day** based on a long-term study of argyria in humans (IRIS).

Carcinogenicity

EPA has placed silver in Class D, not classifiable as to human carcinogenicity (IRIS).

50. THALLIUM

Thallium occurs in nature as a trace compound and is mainly associated with potassium and rubidium. Anthropogenic sources of thallium are gaseous emissions from cement factories, coal burning power plants, metal sewers, and leaching from ore processing operations (OGWDW).

Pharmacokinetics

Thallium has been shown to inhibit enzymatic action in the body. In acute thallium poisoning, human brain areas densely populated with neurons were found to accumulate thallium more than other areas. Thallium excretion is a very slow process mainly occurring via the kidney, gut, and salivary glands (HSDB).

Acute toxicity

Acute exposure to thallium can cause sever paroxysmal abdominal pain, vomiting, and diarrhea. Thallium poisoning often causes an increase in heart rate and blood pressure. Some victims have experienced a loss of vision in industrial exposures. In very severe cases, tremors, delirium, convulsions, hypotension, bradycardia, paralysis, coma, and death can occur (HSDB).

Chronic toxicity

Long-term exposure to thallium causes the relaxation of vascular smooth muscle, increased sympathetic tone, vagus nerve damage, fatty infiltration and necrosis of the liver, nephritis, gastroenteritis, pulmonary edema, degenerative changes in the adrenals, degeneration of peripheral and central nervous system, alopecia, and in some cases death (HSDB). EPA provides RfDs for several forms of thallium, with an **RfD for thallium chloride of 0.00008 mg/kg-day**, which is based on a subchronic study with rats. Because no data are available regarding the forms of thallium most commonly present in the LDW, the conversion factors provided in IRIS were used to convert the RfD for thallium chloride to an RfD for thallium. Thus, the **RfD used in this risk assessment for thallium is 0.00007 mg/kg-day**.

Carcinogenicity

EPA has placed thallium in Class D, not classifiable as to human carcinogenicity.

51. TOXAPHENE

Toxaphene is an organochlorine pesticide that is comprised of a mixture of at least 670 chlorinated camphenes. Toxaphene was probably the most heavily used pesticide in the United States during the 1970s after DDT was banned. It was banned for most uses in 1982; all uses were banned in 1990. However, due to its relatively long half-life, it persists in the environment. The soil half-life is approximately 1 to 14 years (HSDB).

Pharmacokinetics

The components of toxaphene are metabolized in mammals via dechlorination, dehydrodechlorination, and oxidation, primarily through the action of the mixed function oxidase system and other hepatic microsomal enzymes. Conjugation may occur but is not a major route of metabolism. Each component of toxaphene has its own rate of biotransformation, making the characterization of toxaphene pharmacokinetics complex. Some components of toxaphene are highly lipophilic and poorly metabolized; these components may accumulate in body fat (ATSDR 1996).

Acute toxicity

Acute high-level exposures to toxaphene and toxaphene-contaminated food have resulted in death in adults and children with an estimated minimum lethal dose of 2 to 7 g/day, which is equivalent to 29 to 100 mg/kg-day for an adult male. LD50 values in rats were 80 mg/kg-day for females and 90 mg/kg-day for males. Transient liver and kidney effects, and periods of memory loss have been observed in humans after single large oral exposures. In animals, the most sensitive organ is the liver. Toxicity to the central nervous system, kidney, and adrenal glands have also been observed (ATSDR 1996).

Chronic toxicity

IRIS does not provide a discussion of chronic effects of exposure to toxaphene or an RfD. Chronic exposure to toxaphene may result in damage to the following organ systems: liver, kidney, adrenal, immunological, and neurological (ATSDR 1996). Chronic exposure to toxaphene may cause hormonal alterations. A study on chronic exposures found increased levels of hepatic metabolism of the hormones estradiol and estrone and a decrease in their uterotropic action. Some adverse effects of toxaphene that do not occur with a single exposure may result from repeated exposures. Exposures at 0.06 mg/kg-day over 5 weeks caused adrenal hormone reductions, whereas a single dose of 16 mg/kg-day did not cause effects.

Carcinogenicity

Toxaphene is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals (IRIS). However, no conclusive human epidemiological studies are available for toxaphene (ATSDR 1996). Oral administration of toxaphene resulted in an increased incidence of hepatocellular carcinomas and neoplastic nodules in mice, and thyroid tumors in rats (IRIS). The **oral cancer slope factor for toxaphene is 1.1 per mg/kg-day**, based on liver tumors in experimental animals (IRIS).

Toxaphene has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells (Soto et al. 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer. In addition to potential carcinogenic effects, toxaphene may also cause disruption of the endocrine system due to its estrogenic activity (Soto et al. 1994).

52. TRIBUTYLTIN

TBT is one of several organotin compounds that have been used as biocides, disinfectants, and antifoulants. This overview focuses primarily on bis(tri-n-butyltin) oxide (TBTO) because this is the only TBT compound for which the EPA has established an RfD for assessing chronic toxicity to humans and because more toxicological information is available for this compound than for other organotin compounds.

Pharmacokinetics

No studies are available regarding the distribution of tin in human tissues following oral exposure (ATSDR 2005d). Laboratory studies with mammals have shown that organotin compounds are absorbed; studies with rats detected tin compounds in the gastrointestinal tract, kidney, and liver. Rats that orally ingested tin compounds showed the highest concentrations in the liver and kidneys; concentrations in the brain and adipose tissue were 10 to 20 percent of those found in the kidneys and liver (Krajnc et al. 1984). Studies involving trialkyltin compounds show that absorbed compounds are metabolized, with the data suggesting that the liver is the active site and dealkylation the principle metabolic pathway (ATSDR 2005d).

Acute toxicity

There are no controlled studies on the effects of TBTO in humans. The available data demonstrate that TBT is toxic to animals, with LD50 values ranging from 122 to 194 mg/kg-day in rats.

Chronic toxicity

There are no studies on the effects of TBTO in humans. Animal studies have shown effects on the blood and liver, and immunological effects, including thymus atrophy and depletion of T-lymphocytes in the spleen and lymph nodes (ATSDR 2005d). In addition, numerous studies have documented the endocrine-disrupting properties of

TBT in invertebrates, and much of this data can also be applied to humans (DeFur et al. 1999).

EPA's IRIS database provides an **RfD for TBTO of 0.0003 mg/kg-day**, based on a NOAEL of 0.025 mg/kg-day. This was based on a chronic feeding study of rats in which immunologic function analyses for specific and nonspecific resistance were performed after 4 to 6 or 15 to 17 months of exposure to test doses of TBTO ranging from 0.025 to 2.5 mg/kg-day (Vos et al. 1990). The RfD for TBTO can be converted to TBT ion units by multiplying it by the ratio (0.49) of the molecular weights for the two substances. **The resulting RfD for the TBT ion is 0.00015 mg/kg-day**.

Carcinogenicity

TBTO is currently Class D, which is defined as a chemical not classifiable with respect to human carcinogenicity. There are no data documenting the development of cancer in humans following exposure to TBTO. A large number of studies show that TBTO is not genotoxic, and there are no structure-activity relationships suggesting that TBTO might be a carcinogen.

53. VANADIUM

Vanadium compounds are widely distributed in the earth's crust. Elemental vanadium does not occur in nature, but its compounds exist in over 50 different mineral ores and in association with fossil fuels (HSDB). The route of entry of vanadium compounds most commonly seen in industrial exposures is through the respiratory system. Exposures are usually limited to areas where vanadium pentoxide is produced, in steel mills where vanadium pentoxide is used, and in cleaning boilers fired by oil containing vanadium (HSDB).

Pharmacokinetics

Vanadium compounds and metallic vanadium, when absorbed, are rapidly excreted and exhibit low degrees of toxicity, as indicated by minor irritation and lack of systemic effects. Absorbed vanadium is widely distributed in the body. In animals, the highest values are found in bone, kidney, liver, spleen and lung. Bone maintains essentially unchanged levels for several weeks. The lowest values are found in the brain, but in human autopsy material, brain concentrations of vanadium are more or less the same as those found in other organs (HSDB).

Acute toxicity

Vanadium and its compounds are principally eye and respiratory tract irritants that result in conjunctivitis, coughing, wheezing, difficulty in breathing, and industrial bronchitis. A metallic taste and throat irritation may occur. Greenish discoloration of the fingers, scrotum, and upper legs may also be present. A greenish black discoloration of the tongue indicates heavy exposure (HSDB).

Chronic toxicity

Some studies suggest exposure to vanadium may impair the lung resistance to respiratory infection, although the available data on chronic respiratory effects of vanadium are still inconclusive. NCEA provides an **RfD of 0.001 mg/kg-day** for vanadium (EPA 2004).

Carcinogenicity

At this time, there is no information regarding the carcinogenicity of vanadium to humans or animals.

54. ZINC

Zinc is an essential trace element that plays a necessary role in enzymatic functions, protein synthesis, and carbohydrate metabolism. Small doses of zinc are necessary for normal growth and development in birds and mammals. Zinc also has many industrial uses. It is used as a galvanizing agent, component in brass, bronze alloys, light metal alloys, and in wet batteries (HSDB). The most common route of high-level exposure to zinc is through consumption of liquid contained in galvanized metal containers or by water contaminated with industrial zinc waste (ToxFAQs).

Pharmacokinetics

Absorption of zinc occurs in the intestine when ingested or through the lung when zinc dust or fumes are inhaled. Zinc is mainly stored in skeletal muscle, but significant concentrations can also occur in the pancreas, prostate, liver, and retina. Zinc has a biological half-life of 162 to 500 days (HSDB).

Acute toxicity

In humans, ingestion of gram quantities of zinc may cause pancreatic derangement, light-headedness, and mild derangement of cerebellar function. Acute exposure to zinc can also cause dizziness, nausea, tightness in the throat, diarrhea, and vomiting. Metal fume fever has been observed after inhalation of zinc oxide fumes (HSDB).

Chronic toxicity

Prolonged exposure to drinking water that contained 40 mg/L of zinc triggered symptoms such as irritability, muscular stiffness and pain, loss of appetite, and nausea (HSDB). EPA has established an **RfD of 0.3 mg/kg-day for zinc** based on a human diet supplement study in which adult females experienced a 47% decline in erythrocyte superoxide dismutase (ESOD) after 10 weeks of exposure (IRIS).

Carcinogenicity

EPA has placed zinc in Class D, not classifiable as to human carcinogenicity (IRIS).

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