APPENDIX B

Toxicity Profiles

TABLE OF CONTENTS

APPENDIX B – Toxicity Profiles

ACENAPHTHYLENE

See PAH profile.

ALUMINUM

Pharmacokinetics

In general, absorption of aluminum in humans and animals is poor via inhalation or oral exposure pathways and dermal absorption is even less significant (ATSDR, 1999).

Oral Exposure
Absorption of aluminum through normal dietary uptake is estimated as 0.1%, while more bioavailable forms (e.g., complexes with some carboxylic acids) can be absorbed at a rate closer to 1.0%. In addition, the aqueous and pH conditions of the gut will also affect absorption (ATSDR, 1999). Distribution of aluminum following oral exposure in animals has been shown to occur in the brain (hippocampus), while concomitant intake of vitamin D has been found to enhance accumulation and retention of aluminum in the bones, kidneys, muscle and heart (ATSDR, 1999). Elimination of aluminum following oral uptake in humans and animals occurs in the kidneys (via urine) with unabsorbed aluminum being excreted primarily in the feces. A study on rats found a single oral dose of 11 mg aluminum resulted in a 14-fold increase in aluminum levels in the urine within 24-hours of exposure and that normal baseline levels returned after 5 days (ATSDR, 1999).

Inhalation Exposure
Inhalation exposure studies on humans have found occupational exposure to aluminum fumes, dusts and flakes result in increased serum levels, and that direct absorption in the brain may occur through the olfactory tract via axonal transport. Autopsy results from a stonemason exposed to aluminum found elevated concentrations (compared to normal baseline levels) in the lungs, hilar lymph nodes, liver and spleen (ATSDR, 1999). Rats and guinea pigs with intermediate or chronic exposure to aluminum chlorhydrate showed accumulation primarily in the lungs, with some additional accumulation in the adrenal glands and peribronchial lymph nodes. Excretion in humans occurs via urine, and a correlation exists between exposure duration and urinary concentrations; welders exposed to 0.2 to 5.3 mg/m^3 aluminum for 10 years had urinary aluminum half-lives of over 6 months compared to 9 days in individuals with less than 1-year exposure (ATSDR, 1999).

Dermal Exposure
No studies have been found on the absorption of aluminum in humans following dermal exposure, although a mouse study has found elevated concentrations in the liver, brain, lung and kidneys following exposure to 0.04 mg/day for 20 days during gestation (ATSDR, 1999). No studies were found on the excretion of aluminum following dermal exposure in humans or animals (ATSDR, 1999).

Toxicity

Non-Carcinogenic Effects
Studies on the toxicity of aluminum through inhalation, oral or dermal exposure are limited and often contradictory or provide limited information (i.e., do not specify the dose, form or bioavailability of aluminum or the identity and concentration of other compounds with concomitant exposure), making evaluations of aluminum-specific toxicity difficult.

Oral Exposure
Aluminum is ubiquitous in the diet of humans and animals; it is used in food additives, packaging, drinking water and medication. Normal dietary intake in humans is estimated as being 0.10 to 0.12 mg/kg/day in adults (ATSDR, 1999). Toxicity to humans following oral exposure to aluminum phosphide has been reported (including cardiovascular and gastrointestinal effects following acute accidental or suicide-attempt exposure), but is considered to be the result of the formation of highly toxic phosphine gas, rather than the aluminum itself. Numerous oral toxicity studies have been performed on animals, but unfortunately the base rate of dietary intake is often not reported, which underestimates the total intake concentrations. Some effects of aluminum following oral intake in rodents include ataxia, splaying and dragging of hindlimbs, and paralysis in maternal mice exposed to approximately 184 mg/kg/day or 250 mg/kg/day as aluminum lactate during gestation and lactation (ATSDR, 1999).

Oral uptake studies of aluminum found NOAELs ranging from 0.6 mg/kg/day in female mice and all rats, following 5 or 7 weeks (mice) and 2.5 years (rats) exposure to aluminum chloride and aluminum potassium sulfate (administered in food and water) to 979 mg/kg/day in mice (administered in food as aluminum potassium sulfate over 20 months) (ATSDR, 1999). Oral exposure LOAELs ranged from 130 mg/kg/day (administered as aluminum lactate in food over a 6-week period) in female mice (causing decreased total, vertical and horizontal neurological activity; decreased diurnal period and shortened activity periods) to 770 mg/kg/day (administered once via gavage as aluminum chloride) in male mice (corresponding to an LD_{50}) (ATSDR, 1999).

Inhalation Exposure
Toxicity following inhalation exposure has been found in occupational studies and consists of wheezing, dyspnea and impaired lung function (following exposure to

unspecified aluminum fumes) and pulmonary fibrosis following exposure to aluminum-containing dusts, all of these exposures co-occur with exposure to numerous other toxic chemicals (ATSDR, 1999). One individual chronically exposed to aluminum dust and metallic aluminum showed reversible effects on the lungs (sarcoid-like epitheloid granulomas). Neurological effects for chronically-exposed workers are limited to sub-clinical effects including memory impairment, electroencephalogram (EEG) changes, eye-hand coordination, and motor skills, although these studies did not adequately characterize aluminum exposure, and their validity is questioned (ATSDR, 1999). Hamster studies have found absolute lung weight increases following 3-day exposure to = 7 mg/m^3, and correspond to similar findings in rabbits following 43 mg/m^3 exposure for 5 days. Reduction in body weight was observed in a 24-month study in rats exposed to 6.1 mg/m^3 as aluminum chlorhydrate.

Inhalation uptake studies with experimental animals found NOAELs for aluminum ranging from 0.061 mg/m^3 following long-term exposure to aluminum chlorohydrate in rats and guinea pigs to 100 mg/m^3 following 5 days exposure to aluminum powder, for 4 hours/day in male rats (ATSDR, 1999). Inhalation LOAELs ranged from 0.61 mg/m^3 in rats and guinea pigs from exposure to aluminum chlorohydrate over 6 months, 5 days/week, for 6 hours/day (causing increases in alveolar macrophages and lesions in the lungs in both species) to 200 mg/m^3 in male rats following 5 days exposure to aluminum powder (causing multifocal microgranulomas in the lungs) (ATSDR, 1999).

Dermal Exposure
Dermal toxicity studies are limited; effects of aluminum exposure include skin damage in female mice, rabbits and large white pigs following application of 10% aluminum chloride (0.005 to 0.1 g Al) or aluminum nitrate (0.006 to 0.013 g Al), but not other forms following a 5-day exposure study (ATSDR, 1999). Studies on increased incidences of Ahlzheimer's disease following application of aluminum-containing deodorants in humans have found a trend ($p=0.03$) toward a higher risk with increasing use of these deodorants (ATSDR, 1999).

Reference Dose for Chronic Oral Exposure (RfD)
An EPA-NCEA provisional RfD of 1 mg/kg/day has been derived for aluminum (US EPA Region 3, 2003). An RfD for aluminum is not available on US EPA IRIS.

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC is not available for aluminum on US EPA IRIS, however a provisional chronic inhalation reference dose of 1E-3 mg/kg/day is available from the EPA-NCEA (US EPA Region 3, 2003).

Carcinogenic Effects
A carcinogenicity classification for aluminum is not available.

Carcinogenic Risk from Oral Exposure
Carcinogenicity data for aluminum are not available.

Carcinogenic Risk from Inhalation Exposure
Carcinogenicity data for aluminum are not available.

Summary

Oral Chronic RfD_o	1 mg/kg/day	US EPA Region 3, 2003
Inhalation RfD_i	1E-3 mg/kg/day	US EPA Region 3, 2003
Oral Slope Factor	not found	US EPA, 2004
Inhalation Slope Factor	not found	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Toxicological Profile for Aluminum.

United States Environmental Protection Agency (US EPA) Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist.
URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS).
URL: http://www.epa.gov/iris/

ANTHRACENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The pharmacokinetics of anthracene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
The toxicity of anthracene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for anthracene is 0.3 mg/kg/day based on a study where anthracene was administered via gavage to mice at four different doses (0, 250, 500 and 1000 mg/kg/day) for a period of 90 days. The mice were investigated for a number of clinical endpoints including mortality, changes in body weight and food consumption, ophthalmology, hematology and clinical chemistry results, organ weight, organ-to body weight ratios, pathology and histopathology. As no effects related to the administration of anthracene were observed, the highest test dose (1,000 mg/kg/day) was concluded to be the NOAEL. A LOAEL could not be developed from this study. An uncertainty factor of 3000 was applied to the NOAEL, and consisted of a factor of 10 to account for interspecies extrapolation, a factor of 10 to account for interspecies variability and a factor of 30 to account for (a) the use of a subchronic study to develop a chronic RfD, (b) the lack of reproductive/development data and (c) lack of adequate toxicity data in a second species. US EPA indicates that confidence in the study is low (US EPA, 2004). Although the study was well designed to evaluate a variety of toxicological endpoints, the failure to identify a LOAEL prevents a higher degree of confidence from being assigned to the study.

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for anthracene is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified anthracene as a Class D carcinogen – not classifiable as to human carcinogenicity, due to a lack of human data and inadequate data from animal studies. Several animal studies (rats and mice) have been conducted however, none of the

animals developed tumors after administration of anthracene. Appropriate experimental controls were also lacking in several of the studies.

Carcinogenic Risk from Oral Exposure
An oral slope factor for anthracene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for anthracene is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD	0.3 mg/kg/day	NOAEL	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Anthracene. URL:http://www.epa.gov/iris/

ANTIMONY

Pharmacokinetics

Oral Exposure
No studies have been found on the absorption, distribution or excretion of antimony via oral exposure, although animal studies have found at least some forms will be absorbed across the gastrointestinal tract, with estimates for antimony tartrate and trichlorine ranging from 2 to 7% (ATSDR, 1992). The ICRP-derived rate of gastrointestinal absorption in humans is 10% for antimony tartrate and 1% for all other forms (ATSDR, 1992). Distribution in animals following oral exposure to antimony occurs in the gastrointestinal tract, the liver, kidneys, bones, lungs, spleen and thyroid. Dose-response rates of uptake have not been observed and antimony uptake demonstrates a plateau of absorption. Animal studies have found antimony is partially absorbed from the gastrointestinal tract, with either urine or feces as the main route of excretion, depending on the ligand form.

Inhalation Exposure
Absorption via inhalation exposure in humans has not been characterized, although the presence of antimony in the blood and urine following occupational exposure to dust suggest absorption does occur across the lungs (ATSDR, 1992). Particle size (i.e., ligand form) determines the rate of uptake, in addition, mucocilary clearance (swallowing) accounts for gastrointestinal absorption following inhalation exposure. Antimony is mainly transported in the bloodstream and is distributed to various tissues. Excretion occurs via urine in humans, while animals are known to eliminate antimony via feces as well. Animal studies have also shown elimination of antimony (in the form of antimony tartrate) occurs in two phases: the first phase (accounting for 90% of the initial dose) occurs in 24 hours, with the half-life of the second phase taking 16 days (ATSDR, 1992).

Dermal Exposure
Dermal exposure studies were not found for humans, and only limited information was available for animals (ATSDR, 1992). From these studies it is known that at least some antimony is absorbed through the skin; accumulation likely occurs in the liver, kidney, skeleton, spleen and fur; and parenteral exposure studies infer excretion occurs via the urine and feces (ATSDR, 1992).

Toxicity

Non-Carcinogenic Effects
Oral Exposure

One effect to humans following oral exposure to antimony includes vomiting (after an individual ingested approximately 0.53 mg/kg potassium antimony tartrate) (ATSDR, 1992). Reported animal effects include: vomiting, severe diarrhea, mild hematological alterations, and severe weight loss (ATSDR, 1992).

Oral uptake studies of antimony found NOAELs ranging from 0.0748 mg/kg/day for antimony trichloride in rats (administered for 30 days via water, focusing on cardiological effects) up to 16,714 mg/kg/day for antimony trioxide administered for one day via food (ATSDR, 1992). Oral exposure LOAELs ranged from 0.0748 mg/kg/day in rats for antimony trichloride (administered in water over 21 to 81 days), causing decreased hypotensive responses in newborns and decreased maternal weight gain to 16,714 mg/kg/day in rats for antimony trioxide (administered for one day via food) causing diarrhea (ATSDR, 1992).

Inhalation Exposure

Occupational studies on the toxicity of antimony have found exposure to antimony trioxide and/or pentoxide dust (at concentrations = 8.87 mg/m^3) caused pneumoconiosis (lung inflammation due to dust inhalation). A second occupational study found unspecified concentrations of antimony cause pulmonary alterations (including airway obstruction, bronchospasm and hyperinflation) and chronic bronchitis, chronic emphysema, inactive tuberculosis, pleural adhesions and irritation (ATSDR, 1992). Other workplace-related effects included increased blood pressure, degenerative changes in myocardium and electrocardiogram abnormalities, and gastrointestinal, ocular and reproductive effects. Toxicity in animals includes respiratory effects such as pneumoconiosis and increased alveolar macrophages leading to fibrosis, parenchmatous and fatty degeneration of the liver, tubular dilation of the kidneys, ocular conjunctivitis and dermatosis of the eyes, a decreased number of offspring and 67% failure rate for conception (ATSDR, 1992). Lung cancer has also been observed in rats exposed to 4.2 and 36 mg/m^3 antimony trioxide for one year.

Inhalation uptake studies of the effects of antimony on experimental animals found NOAELs ranging from 3.81 mg/m^3 for antimony trisulfide following a 7 weeks of exposure, over 7 hours/day, for 5 days/week in dogs (focusing on cardiological effects) to 799 mg/m^3 for antimony as stibine in studies on rats and guinea pigs over a 30 minute duration (ATSDR, 1992). Inhalation LOAELs for antimony ranged from 0.07 mg/m^3 for antimony trioxide from a 1-year, 5 days/week, 6 hours/day exposure duration study in rats (chronic inflammation and proliferation of macrophages and hyperplasia in peribronciolar lymphnodes) to 1395 mg/m^3 from 30 minutes exposure duration to antimony as stibine in rats and guinea pigs (causing increased mortality and pulmonary edema) (ATSDR, 1992).

Dermal Exposure

No studies were found on the toxicity of antimony to humans through dermal exposure, although animal studies have found lung hyperemia in rabbits exposed to 6 to 8 applications of antimony trioxide paste, localized edema in rabbits given 6685 mg/kg antimony trioxide and eye irritation in rabbits following direct application of 79 to 100 mg antimony trioxide and thioantimonate to the eyes (ATSDR, 1992).

Dermal uptake studies with antimony are limited; NOAEL values included 209 mg and 20,900 mg in rabbits, for antimony pentasulfides and trioxides, respectively (following 13-week and one-day exposure durations) (ATSDR, 1992). Dermal LOAELs (both for antimony trioxide) ranged from 79.2 mg, causing mild eye irritation in rabbits, to 6685 mg/kg causing edema in rabbits. Both studies were over a 1-day exposure period (ATSDR, 1992).

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for antimony is 4E-4 mg/kg/day based on a chronic rat oral bioassay with longevity, blood glucose and cholesterol levels as the critical effects (US EPA, 2004a). A NOAEL value was not determined, but the LOAEL was 0.35 mg/kg body weight/day. The uncertainty factor is 1000 based on interspecies conversion (10), protection of sensitive subpopulations (10), and a factor of 10 because a NOAEL was not established. Confidence in the study, database and RfD value is reported as low based on the use of only one test species, one dose level and lack of a NOAEL and the database is deficient due to the lack of adequate oral exposure studies (US EPA, 2004a)

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for antimony trioxide is 2E-4 mg/m^3 based on a 1-year chronic inhalation exposure study in rats (with a critical effect of pulmonary toxicity and chronic interstitial inflammation) (US EPA, 2004b). A 10% relative increase in effects was used to derive the benchmark concentration (BMC_{10}) of 0.87 mg/m^3, which was then converted to a human equivalent concentration (BMC(HEC)) of 0.074 mg/m^3. The uncertainty factor for this RfC is 300 (based on the protection of sensitive subpopulations (10), interspecies extrapolation following dosimetric scaling (3), database deficiencies (3), and for a less-than-lifetime exposure duration (3)). The confidence in the study, database and RfC value is medium based on the lack of lifetime data and reproductive/ developmental studies in humans (US EPA, 2004b).

Carcinogenic Effects
The US EPA has not classified antimony for carcinogenicity (US EPA, 2004a/b).

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for antimony or antimony trioxide at this time (US EPA, 2004a/b).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for antimony or antimony trioxide at this time (US EPA, 2004).

Summary

Oral Chronic RfD (Al)	4E-4 mg/kg/day	blood effects, longevity	US EPA, 2004a
Inhalation RfC (AlO_3)	2E-4 mg/m^3	respiratory effects	US EPA, 2004b
Oral Slope Factor	not available at this time		US EPA, 2004a/b
Inhalation Slope Factor	not available at this time		US EPA, 2004a/b

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1992. Toxicological Profile for Antimony.

United States Environmental Protection Agency (US EPA). 2004a. Integrated Risk Information System (IRIS) Summary for Antimony. URL: http://www.epa.gov/iris/

US EPA. 2004b. Integrated Risk Information System (IRIS) Summary for Antimony trioxide. URL: http://www.epa.gov/iris/

AROCLOR 1248 AND 1260 (POLYCHLORINATED BIPHENYLS OR PCBS)

Pharmacokinetics

Oral Exposure

Oral exposure through consumption of contaminated food is presumed to be the major route of exposure to polychlorinated biphenyl (PCB) mixtures, including the congeners Aroclor 1248 and 1260, for the general population. Vegetables account for a major part of the intake of lower chlorinated PCB congeners, while foods with a higher fat content, such as fish, dairy products, and meat, play contain greater concentrations of higher chlorinated congeners (ATSDR 2000). Human oral exposure to a PCB mixture revealed a maximum concentration in blood was reached within 2 days of dosing, and declined rapidly thereafter.

PCB metabolism depends primarily on the number and positioning of chlorine atoms and on the animal species; the initial step involves the enzyme-mediated oxidation of arene oxides in the liver by the cytochrome P-450 enzyme family. Depending on the number and position of the chlorine-substitutions, one or more arene oxide intermediates may be formed from a given PCB. Most hydroxylated PCB metabolites are excreted in feces and/or in urine, however, PCB metabolites can also be retained in the body, due to either their high lipophilicity or reversible binding to proteins. The apparent half-life for Aroclor 1248 in humans was estimated as 8.6 years (ATSDR 2000). In monkeys administered a single dose of 1.5 or 3.0 g/kg Aroclor 1248 (via gavage), retention was estimated to be greater than 90%, resulting in a liver concentration twice that found in the kidney and brain (ATSDR 2000). In most other studies, adipose tissue contained the highest PCB concentrations (ATSDR 2000). In humans, absorption from mother's milk to child ranges from 60 to 100% (ATSDR 2000). A number of animal studies demonstrate that PCB mixtures and specific congeners can cross the placental barrier and enter the fetus (ATSDR 2000).

Inhalation Exposure

Inhalation exposure is considered to be a major route of occupational exposure to PCBs (ATSDR 2000). Up to 80% of the levels found in adipose tissue in workers at a capacitor factory may have been absorbed by the inhalation route (ATSDR 2000). Specific information concerning absorption of Aroclor 1248 and 1260 is limited. Accumulation of PCBs is mainly in fatty tissues, with long-term distribution in the adipose, skin, liver and muscle tissues.

Dermal Exposure

The dermal route of exposure was found to be a significant contributor to the accumulation of PCBs in adipose tissue of workers in the capacitor manufacturing

industry (ATSDR 2000). Studies using human cadaver skin showed 2.6, 10, and 43% dose retention after 24 hours exposure to a mix of Aroclor 1242 in soil, mineral oil, and water, respectively (ATSDR 2000). In the rhesus monkey, topical application of Aroclor 1242 in soil resulted in 14% absorption (ATSDR 2000).

Toxicity

Non-Carcinogenic Effects

Oral Exposure

Food consumption is the major source of body burden of PCBs in the general population. Effects in rats exposed orally to 50 mg/kg/day of Aroclor 1248 in acute-duration studies included increased liver weight, decreased liver glucose 6-phosphatase, and/or decreased serum cholesterol (ATSDR 2000). Hepatotoxicity is a primary effect of PCBs (including Aroclors 1248 and 1260). Immune function disorders have also been observed in humans and several animal species (ATSDR 2000). Reproductive and developmental effects including low birth weight and decreased gestational time, and decreased reproductive capacity have also been observed in human and animal species (ATSDR 2000). Experimental animals that consumed low doses of PCBs in food, over several weeks or months, developed various health effects including anemia, acne, and liver, stomach, and thyroid gland injuries (ATSDR 2000). Other effects caused by PCB ingestion in animals include reductions in the immune system function and behavioral alterations. Some PCBs are endocrine disruptors, which mimic or block the action of hormones from the thyroid and other endocrine glands.

Inhalation Exposure

Studies in workers suggest that exposure to PCBs may cause irritation of the nose and lungs and gastrointestinal discomfort. Upper respiratory tract or eye irritation, cough, and tightness of the chest were noted among 326 capacitor workers exposed to 0.007 to 11 mg/m^3 mean air concentrations of a mixture of Aroclor congeners for over 5 years (ATDSR 2000). Gastrointestinal symptoms, joint pain and weight loss were also reported in workers exposed to various Aroclors at mean concentrations of 0.007 to 11 mg/m^3 (ATDSR 2000). Cirrhosis of the liver and increased serum levels of liver-related enzymes have been correlated with serum PCB levels in workers occupationally exposed to PCB levels of 48 to 275 $\mu g/m^3$.

Dermal Exposure

Single dermal applications of high concentrations PCBs caused death in rabbits and mice. Application of Aroclor 1260 to the shaved back skin of female New Zealand rabbits 5 days/week for 28 or 38 days at estimated doses of 42 to 44 mg/kg/day resulted in thickening of the skin and acne lesions (ATSDR 2000).

Reference Dose for Chronic Oral Exposure (RfD)

A general RfD for all PCB congeners is not available. In addition, the US EPA has concluded that the health effects data for Aroclor 1248 are inadequate for the derivation of an oral RfD. Aroclor 1260 is not listed on the US EPA IRIS website (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)

A general RfC for all PCB congeners is also unavailable. The US EPA has also concluded that the health effects data for Aroclor 1248 are inadequate for the derivation of an oral RfC. Aroclor 1260 is not listed on the US EPA IRIS website (US EPA, 2004).

Carcinogenic Effects

PCBs in general (i.e., all congeners) are classified as Class B2 – probable human carcinogen based on insufficient human data and adequate animal data. Statistically significant increased incidences of liver tumours have been found in male (Aroclor 1260 only) and female rats (all congeners) (US EPA, 2004). Studies of several cohorts of workers in capacitor factories have shown increased incidences of cancer, however no correlation between incidence and exposure duration and/or latency could not be determined (US EPA, 2004).

Carcinogenic Risk from Oral Exposure

The US EPA has developed a tiered approach to oral slope factor selection based on likely exposure pathways and duration in addition to the type of PCBs likely to be present at the site. This site classifies as a "high risk and persistence" as most of the following criteria are met: food chain exposure, sediment or soil ingestion, dust or aerosol inhalation, dermal exposure, presence of dioxin-like congeners and early-life exposure (US EPA, 2004). The upper bound estimate, $2.0(mg/kg/day)^{-1}$, for high risk and persistence sites was selected. The upper bound estimate is based on a study that found tumours in rats administered PCB congeners via dietary intake (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure

The US EPA has developed a upper bound inhalation slope factor of 4E-2 $(mg/kg/day)^{-1}$ based on the occurrence of liver carcinomas or adenomas. However, the US EPA indicates that for inhalation of dust or aerosol containing PCBs, the oral slope factor for "high risk and persistence" should be used instead (US EPA, 2004).

Summary

Oral Chronic RfD	not available at this time		US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor (PCB)	2.0 $(mg/kg/day)^{-1}$	liver cancer	US EPA, 2004
Inhalation Slope Factor (PCB)*	0.04 $(mg/kg/day)^{-1}$	liver cancer	US EPA, 2004

* Oral slope factor used to assess soil dust as per US EPA guidance (US EPA, 2004)

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2000. Toxicological Profile for PCBs.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for PCBs. URL: http://www.epa.gov/iris/

ARSENIC

Pharmacokinetics

Oral Exposure
Human studies show that both arsenates and arsenites are well absorbed across the gastrointestinal tract, as demonstrated by the small percentage of arsenic eliminated directly in feces (absorption of insoluble arsenic salts is much lower than that of arsenates and arsenites). Absorption of arsenates and arsenites are estimated to be on the order of 95%. Urinary excretion of arsenates and arsenites ranges from 55 to 80% of the daily intake. Animal studies on arsenic bioavailability indicate the absorption of arsenic ingested in dust or soil is considerably less than the absorption of arsenic from ingested salts (ATSDR, 2000). The bioavailability of arsenic from soil is reduced by low solubility and accessibility due to the presence of other soil matrix components (Davis, 1992 as cited in ATSDR, 2000). A study where arsenic-contaminated soil from mining and smelting sites was incubated in simulated stomach acid found that only a portion of the arsenic (ranging from 3 to 50%) became soluble. The estimates of soluble or bioavailable arsenic agreed well with the bioavailability estimates for the same soil samples.

Inhalation Exposure
Inhaled airborne arsenic is rapidly deposited in the respiratory tract and absorbed into the bloodstream (Hrudey, 1996). The size and solubility of the aerosols containing arsenic influence the extent of deposition, retention and clearance from the lungs. A study of arsenic absorption by inhalation in a group of lung cancer patients indicated that about 40% of the arsenic in the cigarette smoke was deposited in the lungs and absorption was estimated to be 75 to 85 %, resulting in a total absorption of about 30 to 40% of the arsenic in the cigarette smoke. The American Conference of Governmental Industrial Hygienists (ACGIH, 2001) indicates approximately 77% of airborne particles with a diameter of 10 μm are generally deposited in the respiratory tract. The World Health Organization (WHO, 1981; as cited in ATSDR, 2000) indicates that the bioavailability of deposited, water soluble As(III) may be as high as 85 to 90%. Smelter workers exposed to arsenic trioxide absorbed about 40 to 60% of the estimated inhaled dose (Vahter et al, 1986; as cited in ATSDR, 2000). Vahter et al also demonstrated that arsenic urinary elimination is relatively rapid, as urinary arsenic excretion increased within a few hours of the smelter workers beginning work for the week, and decreased over the weekend.

Dermal Exposure
Several studies have been conducted on the absorption of inorganic arsenic through skin in humans and animals. Wester et al. (1993; as cited in Hrudey et al, 1996) studied the absorption of arsenic from water and soil in both humans and monkeys. Absorption of arsenic and arsenic mixed with soil by the skin was tested using radiolabeled arsenic (H_3AsO_4) on cadavers. Only 0.8% of the arsenic in water solution was found to penetrate

human skin in comparison to the 2 to 6% that penetrated the monkey abdominal skin. Three (3) to 4.5 % of the arsenic mixed with soil was absorbed by the monkey skin in comparison to 1.9% absorbed by human skin.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Respiratory effects such as pulmonary edema, respiratory distress and hemorrhagic bronchitis have been reported following cases of acute oral arsenic poisoning resulting from the consumption of doses of 8 mg/kg. These effects may be secondary effects resulting from damage to the cardiovascular system. High oral doses of arsenic have resulted in cardiac arrhythmias (altered heartbeat).

Blackfoot disease, the loss of circulation in the fingers and toes, is the primary effect of chronic arsenic exposure on the cardiovascular system. Blackfoot disease has been demonstrated in an area of Taiwan with elevated arsenic levels in drinking water. However, similar but less severe cases of peripheral vascular disease such as Raynaud's disease, and gangrene of the fingers and toes have been observed in populations chronically exposed to elevated arsenic concentrations in drinking water in Bangledesh, Mexico and Chile (ATSDR, 2000). Peripheral neurophathy, characterized by numbness in hands and feet, is the most common neurological side effect of chronic oral arsenic exposure. Symptoms improve after the exposure stops, but recovery tends to be slow and incomplete (ATSDR, 2000).

Gastrointestinal distress results from oral consumption of inorganic arsenic and symptoms typically include nausea, vomiting and diarrhea (ATSDR, 2000). These symptoms are the result of irritation of the gastrointestinal mucosa and subside several days after the exposure. Depression of the red blood cells (anemia) or white blood cells (leukopenia) is frequently observed in humans exposed orally to arsenic (ATSDR, 2000). Liver cell damage has been noted only in a few cases of acute arsenic poisoning and is not usually associated with chronic, low level oral arsenic exposure. Skin lesions such as hyperkeratinization of the skin on the palms of the hands and soles of the feet, formation of corns and warts and hyper- or hypopigmentation of the skin are the first clinical signs of chronic oral arsenic exposure (ATSDR, 2000).

There is suggestive evidence that arsenic may cause developmental effects. One case of a mother who ingested arsenic at week 30 of pregnancy resulted in the birth of a premature infant who died several days later. High arsenic was found in the baby's liver, kidney and brain. The infant demonstrated severe pulmonary hemorrhaging which was attributed to the arsenic (Lugo et al, 1969 in ATSDR, 2000). More recent studies on the relationship between normal levels of arsenic in drinking water and congenital heart defects and spontaneous abortions were inconclusive because of small population sample sizes and

the presence of multiple contaminants (ATSDR, 2000). Exposure to arsenic dusts in the workplace has resulted in cases of contact dermatitis. Repeated contact to arsenic dust may lead to arsenic sensitization in occupational settings.

Studies have not identified human subpopulations with a particular susceptibility to arsenic. However, it is possible people with a decreased ability to methylate arsenic in the liver, which is the mechanism by which arsenic toxicity is reduced, may be more susceptible (ATSDR, 2000). Reduced capacity of the liver to methylate arsenic could be due to lack of choline or methionine in the diet. Decreased methlylation capacity of the liver does not seem to result from liver disease, at least at low levels of arsenic exposure (ATSDR, 2000).

Inhalation Exposure

Most information on human inhalation exposure to arsenic derives from occupational settings such as smelters and chemical plants, where the predominant form of airborne arsenic is arsenic trioxide dust. Workers exposed to arsenic dusts in air have experienced irritation to the mucous membranes of the nose and throat that may lead to laryngitis, bronchitis, or rhinitis. There is some evidence that inhaled inorganic arsenic may also result in cardiovascular effects. Cohort mortality studies of arsenic-exposed workers at various smelters have all reported increased risk of mortality from cardiovascular disease (i.e., ischemic heart disease and cerebrovascular disease) and peripheral neurological effects. However, several factors (copper and other metal exposure) may have confounded the conclusions. Several case studies have reported nausea, vomiting, and diarrhea in workers with acute arsenic poisoning following occupational inhalation exposure. Dermatitis (hyperpigmentation, folliculitis, and superficial ulcerations) was observed in 11 employees in one department of a Malaysian tin smelter (total of 500 employees in the plant) exposed to mean arsenic oxide concentrations of 0.005 to 0.014 mg As_2O_3/m^3. There are also several studies suggesting that inhalation exposure to arsenic may have caused increased incidences of spontaneous abortion, significant increases in incidences of congenital malformations and significantly decreased average birth weight in female smelter employees in Sweden (ATSDR, 2000).

No studies were located regarding respiratory effects in humans exposed to organic arsenics. Short-term exposure of rats and mice to high concentrations of arsenic caused respiratory distress, and necropsy of animals revealed bright red lungs with dark spots. Respiratory distress was also observed in rats and mice exposed to high levels of arsenic.

Dermal Exposure

Several studies of humans exposed to arsenic dusts in the workplace have reported inorganic arsenic (usually arsenic trioxide) can cause contact dermatitis (erythema and swelling, with papules and vesicles). Application of organic arsenic to the skin of rabbits was reported to result in mild dermal irritation.

Reference Dose for Chronic Oral Exposure (RfD)

An increased incidence of skin lesions and vascular disease such as Blackfoot disease was observed in people who consumed water containing elevated arsenic levels for long periods of time. Based on this population, a NOAEL was determined to be 0.009 mg/L (or 8E-4 mg/kg/day) while a LOAEL was found to be 0.17 mg/L arsenic (~0.014 mg/kg/day) (US EPA, 2004). The US EPA has developed an oral reference dose of 3E-4 mg/kg/day by dividing the NOAEL by a safety factor of 3 in order to account for insufficient data on the potential effects of arsenic on reproductive toxicity (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)

A reference concentration for chronic inhalation exposure is not available for arsenic at this time (US EPA, 2004).

Carcinogenic Effects

Human epidemiological studies indicate that exposure to arsenic may increase the risk of cancer. Lung cancer is the primary cancer caused by inhalation exposure as demonstrated in workers. Risk of cancer is dependent on exposure level and duration of exposure. Skin cancer in the primary carcinogenic effect that results from oral exposure to arsenic as demonstrated by epidemiological studies on human populations exposed to elevated levels of arsenic in drinking water. Secondary types of cancer that can be caused by oral exposure to arsenic include liver, bladder, kidney and lung). The US EPA has classified inorganic arsenic as Class A – known human carcinogen by inhalation and oral exposure (US EPA, 2004).

Carcinogenic Risk from Oral Exposure

The US EPA has developed a cancer slope factor of 1.5 $(mg/kg/day)^{-1}$ for oral exposure, which is based on studies that indicate an increased incidence of skin cancer in Taiwanese populations that were orally exposed to arsenic in drinking water. (Tseng et al., 1968; Tseng, 1977 in US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure

Adverse effects from dermal exposure to organic and inorganic arsenic have not been well studied. The inhalation unit risk factor for arsenic was also determined by the US EPA (US EPA, 2004) and is based on increased lung cancer incidence in workers occupationally exposed to arsenic via inhalation of dusts in epidemiological studies. The inhalation unit risk factor is 4.3E-3 $(\mu g/m^3)^{-1}$ based on the results of several studies of workers occupationally exposed to arsenic trioxide dust.

Summary

Oral Chronic RfD	3E-4 mg/kg/day	skin lesions	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	1.5 $(mg/kg/day)^{-1}$	skin cancer	US EPA, 2004
Inhalation Unit Risk	4.3E-3 $(\mu g/m^3)^{-1}$	lung cancer	US EPA, 2004

References

American Conference of Government and Industrial Hygienists (ACGIH), 2001. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices.

Agency for Toxic Substances and Disease Registry (ATSDR). 2000. Toxicological Profile for Arsenic.

Hrudey, S.E., W. Chen and C.G. Rousseaux. 1996. Bioavailability in Environmental Risk Assessment. CRC Press, Lewis Publishers, Boca Raton.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Arsenic. URL: http://www.epa.gov/iris/

BARIUM

Pharmacokinetics

Oral Exposure

Oral exposure is thought to be the main route of barium exposure in humans (ATSDR, 1992). Absorption of barium through the gastrointestinal tract is though to be very poor, and has been estimated as <5% (ATSDR, 1992). Rat experiments have found younger animals (<22 days old) absorb approximately 10 times more barium chloride from the gastrointestinal tract (63 to 84%) compared to older animals (approximately 7%). In dogs, serum levels of barium indicate peak absorption from the gastrointestinal tract is within 1 hour. The distribution of barium through oral exposure is similar to inhalation exposure, with 93% accumulating in the bones and teeth. Barium is not metabolized by the body, but may be transported and incorporated into metabolic complexes or body tissues. As barium is poorly absorbed in humans, the majority of orally administered barium is excreted in the feces, with approximately 3% excreted in urine.

Inhalation Exposure

The rate and extent of barium absorption by inhalation has not been characterized for humans, although studies on experimental animals have been performed. In hamsters, 65% of barium deposited in the nasal region as barium chloride is eventually absorbed into the body (ATSDR, 1992). A study on dogs found approximately 50% of barium inhaled as barium chloride and 75% of barium inhaled as barium sulfate is deposited in the pulmonary region, approximately 25% is transported to the skeleton, and the remainder is excreted in urine and feces within 2 weeks. The biological half-life of barium is 8 days in dogs and 10 days in rats. Studies on barium distribution through inhalation exposure in humans have determined that barium primarily deposits in the skeleton and teeth. Dogs inhaling radioactive barium chloride exhibited 70% deposition in the lungs and internal organs (44% in skeleton, 13% in urine and 13% in feces) with minor deposition in the blood (1%) and muscle (4%). No studies have been found on the excretion of barium in humans, but <1% of inhaled barium chloride remains in dogs after 5 days.

Dermal Exposure

No studies have been found on humans on the absorption, distribution or excretion of barium through dermal exposure. One animal study showed that barium applied to the skin of piglets was found in the various layers of the skin (ATSDR 1992). Barium is not expected to cross the intact skin because of the high polarity of the forms in which it is most commonly encountered.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
The majority of barium toxicity studies on humans are from oral exposure studies. Effects following acute exposure include respiratory weakness and paralysis (requiring mechanical ventilation), hypertension and abnormal heart rhythm, gastrointestinal disturbances, progressive muscle weakness leading to partial or total paralysis, degeneration of the kidneys and acute renal failure, and in the most severe cases, death by cardiac arrest or gastrointestinal hemorrhage. Experimental animal studies have found accumulation of fluid in the trachea in rats (following acute exposure), and increased blood pressure following oral exposure.

Oral uptake studies on experimental animals found NOAELs for barium chloride administered in drinking water ranging from 0.054 mg/kg/day in rats (focusing on cardiovascular effects) to 198 mg/kg/day in rats (the same rate had no effect on the cardiovascular, hematological, or immunological systems) (ATSDR, 1992). Barium LOAELs from oral uptake studies of barium chloride range from 0.54 mg/kg/day in rats (causing increased blood pressure) to 277 mg/kg/day in rats (causing death in 50% of males).

Inhalation Exposure
Inhalation of barium sulfate dust by humans has been shown to have minor effects on the lungs (benign pneumonoconiosis). Studies in animals have found pulmonary lesions in rats following intermediate exposure to 3.6 mg/m^3 barium carbonate dust and bronchoconstriction in guinea pigs following 0.06 mg/m^3/min exposure to aerolosolized barium chloride for an unspecified period (ATSDR, 1992).

Dermal Exposure
Barium oxide dust is considered to be a dermal irritant (US EPA 1997). Barium salts would be expected to have a local effect on skin surfaces and would not likely be absorbed systematically to any great extent. Available studies include a case report of an individual exposed dermally to molten barium chloride, a skin irritation study evaluating barium carbonate in experimental animals, and a skin-painting study in which mice were exposed dermally to a barium hydroxide extract of tobacco leaf (ATSDR 1992). The dermal burns that developed in the individual exposed to molten barium chloride may potentially have contributed to abnormal electrocardiogram, vomiting, depressed plasma potassium and increased plasma barium levels. Rats and rabbits exposed to topical barium carbonate showed signs of skin ulceration.

Reference Dose for Chronic Oral Exposure (RfD)

The RfD for barium is 0.07 mg/kg/day based on NOAELs of 10 and 7.3 mg/L (adjusted to 0.21 mg/kg/day). A weight-of-evidence approach was employed to derive the RfD, which used an experimental study and an epidemiological study on humans, and sub-chronic and chronic rat studies. The two human studies found no effects in adults. The sub-chronic and chronic rat studies found NOAELs of 65 and 45 mg/kg/day and LOAELs of 115 and 75 mg/kg/day for renal effects (increased kidney weights). A total uncertainty factor of 3 is applied, made up of an UF of 1 to account for some database deficiencies, and a factor of 3 to account for the lack of potential differences between adults and children and adequate developmental toxicity studies. Confidence in the oral RfD for barium is reported as medium for the quality of the study, database and RfD value.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The inhalation RfC is not available, although human and animal inhalation studies suggest the respiratory system is a target of barium toxicity (US EPA, 2004). An RfD_i has been established from an alternate HEAST table, with a value of 1.4E-4 mg/kg/day (EPA Region 3, 2003).

Carcinogenic Effects
Barium is considered a Class D carcinogen – not classifiable as to human carcinogenicity. This classification is based on the lack of adequate inhalation studies, although barium is still considered not likely to be carcinogenic to humans following oral exposure (US EPA, 2004).

Carcinogenic Risk from Oral Exposure
An oral slope factor is unavailable for barium.

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is unavailable for barium.

Summary

Oral chronic RfD	0.07 mg/kg/day	kidney effects	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Inhalation RfD_i	1.4E-4 mg/kg/day		US EPA Region 3, 2003
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1992. Toxicological Profile for Barium.

United States Environmental Protection Agency (US EPA). 1997. Toxicity Summary for Barium. Risk Assessment Information System. URL: http://risk.lsd.ornl.gov/tox/profiles/barium_f_V1.shtml

US EPA Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Antimony trioxide. URL: http://www.epa.gov/iris/.

BENZENE

Pharmacokinetics

Oral Exposure
No data were found for the distribution of orally administered benzene in humans. In rats, unconjugated benzene metabolites (i.e, hydroquinone) appeared in the liver, kidney, and blood while conjugated metabolites (e.g., phenyl sulfate) appeared primarily in the blood, bone marrow, oral cavity, kidney and liver. Studies quantifying the excretion of benzene and its metabolites by rabbits given oral doses of benzene, revealed that the animals eliminated approximately 40% of the dose as unchanged benzene in exhaled air and about 35% in the urine. Similar patterns of excretion have been observed for humans, cats and dogs, rats, and mice (ATSDR, 1997). In humans and rats, the excretion of benzene in expired air appears to biphasic.

Inhalation Exposure
Inhaled benzene is absorbed rapidly in humans and animals. In several inhalation studies uptake was 47-70% and retention was approximately 30% (ATSDR 1997). Animal data also confirm that benzene is absorbed rapidly through the lungs. Absorbed benzene is distributed throughout the body with most accumulation in adipose tissue. In rats and pregnant mice exposed to benzene concentrations the parent compound and its metabolites were found in lipid-rich tissues, such as brain and fat, and in well-perfused tissues such as the lungs, liver, kidney, and spleen as well as in the fetuses and placenta (ATSDR 1997). Metabolites of benzene (phenol, catechol, and hydroquinone) were detected in the blood and in the bone marrow, where levels of the metabolites exceeded those in the blood (ATSDR, 1997). The levels of phenol in the blood and bone marrow declined more rapidly than did those of catechol or hydroquinone, suggesting that catechol and hydroquinone may accumulate in the body. It appears that benzene metabolism is similar for different routes of administration and for different species, including humans (ATSDR, 1997). Benzene metabolites are excreted primarily in the urine, while unmetabolized benzene is exhaled (ATSDR, 1997).

Dermal Exposure
Recent studies have indicated that absorption of benzene through the skin may be a significant route of exposure, particularly for workers. It has been estimated that employees in tire-building operations could absorb 17 to 40% of total benzene dose through skin and inhalation (ATSDR, 1997). For dermal application of benzene to the skin of male rats revealed the kidney, liver, and treated skin as target sites (ATSDR, 1997).

Toxicity

Non-Carcinogenic Exposure

Oral Exposure

Limited data show that non-lethal oral doses of benzene can impact the nervous, hematological, and immunological systems. Ingested benzene produces symptoms of neurotoxicity at acute doses of 2 mL for humans and 325 mg/kg for rats (ATSDR, 1997). Rats and mice exposed to benzene via gavage developed dose-related lymphocytopenia at 25 mg/kg/day and hyperplasia of the bone marrow (US EPA, 1992).

Inhalation Exposure

The targets for non-lethal concentrations of inhaled benzene include the nervous, hematological, and immunological systems. Neurological symptoms in humans may appear at exposure concentrations of 2237 mg/m^3 (ATSDR, 1997). In animals, 1 week of exposure to 959 mg/m^3 induced behavioral effects, and one to four weeks of exposure to benzene concentrations ranging from 67 to 160 mg/m^3 suppressed the bone marrow, cellular immune response, and the humoral immune response. Inhalation of benzene vapor concentrations of 63,900 mg/m^3 for 5-10 minutes can be fatal to humans; death results from central nervous system depression (US EPA, 1992).

Subchronic and chronic exposures to benzene vapors induce a progressive depletion of the bone marrow and dysfunction of the hematopoietic system. A group of patients exposed to benzene concentrations of 497 to 2077 mg/m^3 for 4 months to 15 years exhibited severe blood dyscrasias and eight of the 32 patients died with thrombocytopenic hemorrhage and infection. These human data are supported by animal data showing bone marrow suppression in mice and rats exposed to benzene concentrations ranging from 32 mg/m^3 for 24 weeks to 959 mg/m^3 for 13 weeks (ATSDR, 1997). Benzene may also have long-term effects on the central nervous system. Workers exposed to benzene for 0.5 to 8 years exhibited electroencephalograph (EEG) changes, atypical sleep activity consistent with neurotoxicity, and peripheral nerve damage. In humans, benzene crosses the placenta and is present in the umbilical cord blood in amounts equal to those in maternal blood; however, studies of the effects of benzene on human reproduction and development have been confounded by the presence of other chemicals in the environment (ATSDR, 1997). Benzene does produce developmental effects (fetal toxicity, but not malformations) in the offspring of treated animals, mostly at doses toxic to the mother (ATDSR, 1997).

Dermal Exposure

Dermal exposure to benzene may cause dryness, irritation and dermatitis (ATSDR, 1997).

Reference Dose for Chronic Oral Exposure (RfD)

The reference dose for chronic oral exposure to benzene is 4E-3 mg/kg/day from a human occupational inhalation study measuring decreased lymphocyte count as the critical effect. A benchmark modeling dose (BMD) approach was used assess experimental

animal and human occupational inhalation studies to derive a benchmark dose level (BMDL) of 1.2 mg/kg/day (from the rat gavage study, most sensitive endpoint) (US EPA, 2004). The BMDL was derived by route-to-route extrapolation with the assumptions that inhalation absorption was 50% and oral absorption was 100% in the dose range near the BMC. The overall uncertainty factor of 300 is comprised of a factor of 3 for effect-level extrapolation, a factor of 10 for sensitive subpopulations, and a factor of 3 for subchronic-to-chronic extrapolation, and an additional factor of 3 for database deficiencies. Overall confidence in the RfD is medium.

Reference Concentration for Chronic Inhalation Exposure (RfC)

The reference concentration for chronic inhalation exposure to benzene is 3E-2 mg/m^3 and is derived from a human occupational inhalation study measuring decreased lymphocyte count as a critical effect. A BMCL of 8.2 mg/m^3 was derived from the study and an uncertainty factor of 300 applied to derive the RfD (US EPA, 2004). The overall uncertainty factor is comprised of factors for effect-level extrapolation (3), for sensitive subpopulations (10), for subchronic-to-chronic extrapolation (3), and for database deficiencies (3).

Carcinogenic Effects

Benzene is classified as being Class A – known carcinogen by the US EPA based on several studies of increased incidence of nonlymphocytic leukemia from occupational exposure, increased incidence of neoplasia in rats and mice exposed by inhalation and gavage (US EPA, 2004). Benzene is carcinogenic in humans and animals by inhalation and in animals by the oral route of exposure. Occupational exposure to benzene has been associated mainly with increased incidences of acute myeloblastic or erythroblastic leukemias and chronic myeloid and lymphoid leukemias among workers (ATDSR 1997). A historical prospective mortality study of chemical workers described a dose-response relationship between exposure to benzene and lymphatic and hematopoietic cancers, adding strength to the association between exposure in the workplace and cancer development (US EPA 1992).

Carcinogenic Risk from Oral Exposure

The US EPA has developed an oral slope factor ranging from of 1.5E-2 to 5.5E-2 $(mg/kg/day)^{-1}$, based on human leukemia epidemiological data from occupational inhalation exposure to benzene (US EPA 2004). The upper end of this range, 5.5E-2 $(mg/kg/day)^{-1}$was selected for use in this risk assessment.

Carcinogenic Risk from Inhalation Exposure

The US EPA has developed inhalation unit risk values ranging from 2.2E-6 to 7.8E-6 $(\mu g/m^3)^{-1}$ based on an epidemiological study of leukemia incidence workers occupationally exposed to benzene (US EPA, 2004). The upper end of the range 7.8E-6 $(\mu g/m^3)^{-1}$ was used in this risk assessment.

Summary

Oral chronic RfD	4 E-3 mg/kg/day	decreased lymphocytes	US EPA, 2004
Inhalation RfC	3 E-2 mg/m^3	decreased lymphocytes	US EPA, 2004
Oral slope factor	5.5E-2 $(mg/kg/day)^{-1}$	leukemia	US EPA, 2004
Unit Inhalation risk	7.8E-6 $(\mu g/m^3)^{-1}$	leukemia	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological Profile for Benzene.

United States Environmental Protection Agency (US EPA). 1992. Toxicity Summary for Benzene. Risk Assessment Information System.
URL: http://risk.lsd.ornl.gov/tox/profiles/benzene.shtml - te

US EPA. 1997. Response to Peer Review. Support Document to Carcinogenic Effects of Benzene: An Update. Prepared by the National Center for Environmental Assessment. June. EPA/600/P-97/001A.

US EPA. 1998. Carcinogenic Effects of Benzene: An Update. Prepared by the National Center for Environmental Assessment. April. EPA/600/P-97/001F.

US EPA. 2002. Toxicological Review of Benzene (Non-Cancer Effects). October. EPA/635/R-02/001F.

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Benzene. URL: http://www.epa.gov/iris/

BENZO(A)ANTHRACENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The pharmacokinetics of benz(a)anthracene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
The toxicity of benz(a)anthracene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD for benz(a)anthracene is not available at this time (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for benz(a)anthracene is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified benz(a)anthracene as Class B2 – probable human carcinogen. Several animal studies in mice have been conducted; animals developed tumors after administration of benz(a)anthracene by gavage, intraperitoneal, subcutaneous or intramuscular injection and topical application (US EPA, 2004). Mutations in bacteria and mammalian cells as well as transformed cells in mammalian cultures were also observed as the result of benz(a)anthracene administration. Carcinogenic assessment of benz(a)anthracene was conducted using a toxic equivalency factor (TEF) approach. Some PAHs are assigned carcinogenicity relative to benzo(a)pyrene (see PAH toxicity profile for explanation).

Carcinogenic Risk from Oral Exposure
An oral slope factor for benz(a)anthracene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for benz(a)anthracene is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD	not available at this time	US EPA, 2004
Inhalation RfC	not available at this time	US EPA, 2004
Oral Slope Factor	not available at this time	US EPA, 2004
Inhalation Slope Factor	not available at this time	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Benz(a)anthracene. URL: http://www.epa.gov/iris/

BENZO(A)PYRENE

Pharmacokinetics

Oral Exposure
Rats given benzo(a)pyrene in starch solution in the diet absorbed 60%. The absorption of benzo(a)pyrene from the gastrointestinal tract of mice and cats was found to be improved when solubilized in lipophilic vehicles (US EPA, 1994). Once benzo(a)pyrene has entered the small intestine, it is solubilized by bile salts and absorbed. Approximately 10 to 20% of an intragastric dose of benzo(a)pyrene entered the thoracic lymph duct in rats. Benzo(a)pyrene can also cross the placenta following oral administration; this is consistent with the observed toxicity in the fetuses and offspring of maternally exposed rodents (ATSDR, 1995).

Inhalation Exposure
Rats exposed to benzo(a)pyrene by inhalation, showed near complete absorption following a 2-week monitoring period (US EPA, 1994). Absorption of inhaled benzo(a)pyrene appears to occur through the mucous lining of bronchi. Distribution of absorbed benzo(a)pyrene is rapid, with high levels found in the liver, esophagus, small intestine, and blood (US EPA, 1994). Benzo(a)pyrene is metabolized by the microsomal cytochrome P-450 monooxygenase system to several arene oxides. Arene oxides may rearrange to phenols, undergo hydration to trans-dihydrodiols, or react with glutathione. 6-hydroxybenzo(a)pyrene, a phenolic metabolite, is further oxidized to the 1,6-, 3,6-, or 6,12-quinones. The phenols, quinones, and dihydrodiols can be detoxified by conjugation to glucuronides and sulfate esters. The dihydrodiols may also undergo further oxidative metabolism. 7,8-diol-9,10-epoxide, is believed to be the primary carcinogenic metabolite of benzo(a)pyrene. The main routes of excretion are hepatobiliary, with elimination in the feces (US EPA, 1994). Benzo(a)pyrene does not appear to be eliminated via expired air.

Dermal Exposure
A 3% *in vitro* application of benzo(a)pyrene was absorbed by human skin following 24 hours of exposure. Among animals, permeation in mice was highest (10%) and lowest in the guinea pig (0.1%). Following dermal exposure, elimination of PAHs occurs rapidly in the urine and feces of guinea pigs and rodents. Essentially all of the radioactivity was recovered in the feces of mice that had been treated topically with radiolabeled benzo(a)pyrene.

Toxicity

Major effects of exposure to benzo(a)pyrene include the induction of cancerous tumors, and effects on the reproductive and immune systems.

Oral Exposure

No data are available on the systemic effects of oral exposure to benzo(a)pyrene in humans. Dietary administration of benzo(a)pyrene has produced papillomas and carcinomas of the forestomach in mice. In mice, genetic differences appear to influence the toxicity of benzo(a)pyrene. Subchronic dietary administration of (120 mg/kg) benzo(a)pyrene for up to 180 days resulted in decreased survival due to bone narrow depression in a "nonresponsive" strain of mice (i.e., a strain whose cytochrome P-450 mediated enzyme activity is not induced as a consequence of PAH exposure). No adverse effects were noted in "responsive" mice (i.e., a strain capable of inducing increased cytochrome P-450 mediated enzyme activity as a consequence of PAH exposure). *In utero* exposure to benzo(a)pyrene has produced adverse developmental/reproductive effects in mice and dietary administration of doses as low as 10 mg/kg during gestation caused reduced fertility and reproductive capacity in offspring, and treatment by gavage with 120 mg/kg/day during gestation caused stillbirths, resorptions, and malformations (ATSDR, 1995). The results of two oral studies in mice and one in rats indicate that benzo(a)pyrene induces reproductive toxicity in animals. The incidence and severity of these effects depends on the strain, method of administration, and dose levels used. Acute exposure time oral studies on benzo(a)pyrene in mice found NOAELs ranging from 10 mg/m^3 (reproductive endpoints) to 150 mg/m^3 (several systemic endpoints) (ATSDR, 1995). LOAELs for acute exposure in mice were 33.3 mg/m^3 (gastric neoplasms) to 160 mg/m^3 (reproductive endpoints). Intermediate exposure time oral studies on benzo(a)pyrene in mice found NOAELs ranging from 1.3 mg/m^3 (gastric tumours) to 133.3 mg/m^3 (reproductive endpoints) (ATSDR, 1995). LOAELs for intermediate exposure in mice were 2.6 mg/m^3 (gastric cancer) to 120 mg/m^3 (systemic endpoints).

Inhalation Exposure

Epidemiologic studies have shown associations between exposure to mixtures of PAHs containing benzo(a)pyrene (e.g., coke oven emissions, roofing tar emissions, and cigarette smoke) and increased risk of lung cancer and other tumors in humans. However, each of the mixtures also contained other potentially carcinogenic PAHs, therefore, it is not possible to evaluate the contribution of benzo(a)pyrene to the carcinogenicity of these mixtures (US EPA, 1994). One study evaluated the respiratory health of 667 workers and found statistically significant decreases in ventilatory function following prolonged exposure, as assessed by duration of employment, to areas of elevated benzo(a)pyrene. Other symptoms included vomiting, breathing problems, chest pains, chest and throat irritation, and coughing. However, no attempt was made to separate the effects of exposure to benzo(a)pyrene and particulate matter, or to identify possible simultaneous exposure to other toxic chemicals. Exposure by inhalation has resulted in benign and malignant tumors of the respiratory and upper digestive tracts of hamsters. A dose-related decrease in survival was noted in hamsters after 60 weeks of inhalation exposure to 46.5 mg/m^3 benzo(a)pyrene (ATSDR, 1995). This reduction in survival was partially attributed to toxic and carcinogenic effects induced by benzo(a)pyrene (e.g., tumors in

the pharynx and larynx that could have inhibited food intake). A significant increase in all lung tumors and a dose-dependent increase in malignant lung tumors for mice exposed to PAH-enriched exhausts containing 0.05 or 0.09 mg/m^3 benzo(a)pyrene was found. Respiratory tract tumors were induced in the nasal cavity, pharynx, larynx, and trachea in a dose-related manner in hamsters exposed to 9.5 mg/m^3 or 46.5 mg/m^3 benzo(a)pyrene for 109 weeks. No lung tumors were found.

Dermal Exposure
Numerous topical application studies have shown that benzo(a)pyrene induces skin tumors in several species, with mice appearing to be the most sensitive species (ATSDR, 1995). Benzo(a)pyrene also acts as an initiator of skin tumors.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD is not available at this time for benzo(a)pyrene (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC is not available at this time for benzo(a)pyrene (US EPA, 2004).

Carcinogenic Effects
Benzo(a)pyrene is classified as Class B2 – probable human carcinogen (US EPA, 2004). Human data specifically linking benzo(a)pyrene to a carcinogenic effect are lacking. There are, however, multiple animal studies in many species demonstrating benzo(a)pyrene to be carcinogenic following administration by numerous routes.

Carcinogenic Risk from Oral Exposure
An oral slope factor of 7.3 $(mg/kg/day)^{-1}$ has been derived for benzo(a)pyrene based on forestomach, squamous cell papillomas and carcinomas in mice. Benzo(a)pyrene was administered in the diet to CFW-Swiss mice resulting in increased incidences of stomach tumors. Concentrations used ranged from 0, 1, 10, 20, 30, 40, 45, 50, 100 and 250 ppm in the diets of male and female mice. The age of the mice ranged from 17-180 days old and the treatment time from 1-197 days. No forestomach tumors were reported in the 0-, 1- and 10-ppm dose groups. The incidence of forestomach tumors in the 20-, 30-, 40-, 45-, 50-, 100- and 250-ppm dose groups were 1/23, 0/37, 1/40, 4/40, 23/34, 19/23 and 66/73, respectively. The authors felt that the increasing tumor incidences were related to both the concentration and the number of doses administered.

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available at this time for benzo(a)pyrene (US EPA, 2004), although a provisional value of 3.1 $(mg/kg/day)^{-1}$ has been assigned by US EPA Region 3 (US EPA, 2003).

Summary

Oral chronic RfD	not available at this time	US EPA, 2004
Inhalation RfC	not available at this time	US EPA, 2004
Oral Slope Factor	7.3 $(mg/kg/day)^{-1}$ stomach cancer	US EPA, 2004
Inhalation Slope Factor	not available at this time	US EPA, 2004
Inhalation Slope Factor	3.1 $(mg/kg/day)^{-1}$ (provisional value)	USEPA Region 3, 2003

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for PAHs.

United States Environmental Protection Agency (US EPA). 1994. Toxicity Summary for Benzo(a)pyrene. Risk Assessment Information System. URL:http://risk.lsd.ornl.gov/tox/profiles/bap_c.shtml

US EPA Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Benzo(a)pyrene. URL:http://www.epa.gov/iris/

BENZO(B)FLUORANTHENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The pharmacokinetics of benzo(b)fluoranthene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
The toxicity of benzo(b)fluoranthene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD for benzo(b)fluoranthene is not available at this time (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for benzo(b)fluoranthene is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified benzo(b)fluoranthene as Class B2 – probable human carcinogen (US EPA, 2004). Although no human data were available, there is sufficient indication from animal bioassay data that benzo(b)fluoranthene will likely cause cancer in humans. Tumors were observed in mice administered benzo(b)fluoranthene via lung implantation, intraperitoneal and subcutaneous injection, and skin painting (US EPA, 2004). Carcinogenic assessment of benzo(b)fluoranthene was conducted using a toxic equivalency factor (TEF) approach. Some PAHs are assigned carcinogenicity relative to benzo(a)pyrene (see PAH toxicity profile for explanation).

Carcinogenic Risk from Oral Exposure
An oral slope factor for benzo(b)fluoranthene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for benzo(b)fluoranthene is not available at this time (US EPA, 2004).

Summary

Oral chronic RfD	not available at this time	US EPA, 2004
Inhalation RfC	not available at this time	US EPA, 2004
Oral Slope Factor	not available at this time	US EPA, 2004
Inhalation Slope Factor	not available at this time	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Benzo(b)fluoranthene. URL: http://www.epa.gov/iris/

BENZO(G,H,I)PERYLENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The pharmacokinetics of benzo(g,h,i)perylene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
The toxicity of benzo(g,h,i)perylene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD for benzo(g,h,i)perylene is not available at this time (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for benzo(g,h,i)perylene is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified benzo(g,h,i)perylene as a Class D carcinogen – not classifiable as to human carcinogenicity, due to a lack of human data and inadequate data from animal studies. Several animal studies (rats and mice) have been conducted however, the number of tumors that animals developed after administration of benzo(g,h,i)perylene were either not statistically significant or only developed in the presence of another carcinogen. Benzo(g,h,i)perylene has caused for forward and reverse mutations in strains of Salmonella as well as DNA damage in Chinese hamster ovary cells (US EPA, 2004). Carcinogenic assessment of benzo(g,h,i)perylene was conducted using a toxic equivalency factor (TEF) approach. Some PAHs are assigned carcinogenicity relative to benzo(a)pyrene (see PAH toxicity profile for explanation).

Carcinogenic Risk from Oral Exposure
An oral slope factor for benzo(g,h,i)perylene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for benzo(g,h,i)perylene is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD	not available at this time	US EPA, 2004
Inhalation RfC	not available at this time	US EPA, 2004
Oral Slope Factor	not available at this time	US EPA, 2004
Inhalation Slope Factor	not available at this time	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Benzo(g,h,i)perylene. URL: http://www.epa.gov/iris/

BENZO(K)FLUORANTHENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The pharmacokinetics of benzo(k)fluoranthene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
The toxicity of benzo(k)fluoranthene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD for benzo(k)fluoranthene is not available at this time (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for benzo(k)fluoranthene is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified benzo(k)fluoranthene as Class B2 – probable human carcinogen (US EPA, 2004). Although no human data were available, there is sufficient indication from animal bioassay data that benzo(k)fluoranthene may cause cancer in humans. Tumors were observed in mice administered benzo(k)fluoranthene via lung implantation and when administered with a promoting agent, in skin painting (US EPA, 2004). Bacteria studies also indicate that benzo(k)fluoranthene is mutagenic. Quantitative estimates of slope factors or unit risk values are not available at this time (US EPA, 2004). Carcinogenic assessment of benzo(k)fluoranthene was conducted using a toxic equivalency factor (TEF) approach. Some PAHs are assigned carcinogenicity relative to benzo(a)pyrene (see PAH toxicity profile for explanation).

Carcinogenic Risk from Oral Exposure
An oral slope factor for benzo(k)fluoranthene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for benzo(k)fluoranthene is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD	not available at this time	US EPA, 2004
Inhalation RfC	not available at this time	US EPA, 2004
Oral Slope Factor	not available at this time	US EPA, 2004
Inhalation Slope Factor	not available at this time	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Benzo(k)fluoranthene. URL: http://www.epa.gov/iris/

BERYLLIUM

Pharmacokinetics

Oral Exposure
Although no human data are available regarding the absorption of beryllium through oral exposure, animal studies show beryllium is poorly absorbed though the gastrointestinal tract (ATSDR, 2000).

Inhalation Exposure
Inhaled beryllium is absorbed through the lungs, however insufficient data are available to quantify the rate and extent of absorption (ATSDR, 2000). Beryllium absorption is greatest in the lungs, followed by the brain, kidney, spleen, liver, heart and bone. Biotransformation of beryllium does not occur during metabolism. The biological half-life of beryllium in serum is estimated to be between 2 to 8 weeks.

Dermal Exposure
Beryllium does not appear to be absorbed through intact skin as exposed workers only demonstrated skin ulcerations when the skin was cut accidentally (ATSDR, 2000).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
No human data are available regarding ingestion of beryllium, however animal studies show lesions on the stomach as well as the small and large intestines as the result of ingestion of beryllium sulfate in the diet.

Inhalation Exposure
Inhalation of high concentrations of soluble beryllium compounds has caused pneumonia in occupationally exposed workers. Chronic inhalation exposure to somewhat lower concentrations can lead to an obstructive lung disease known as chronic beryllium disease (CBD). Chronic beryllium disease is caused by genetically regulated cell-mediated immune responses. Air concentrations of beryllium ranging from 0.52 to 1.04 $\mu g/m^3$ were measured in the few studies, which examined the prevalence of chronic beryllium disease in occupationally exposed workers. One study examined the prevalence of chronic beryllium disease in residents living at least 0.75 miles away from a beryllium factory and found no cases of the disease (ATSDR, 2000). The beryllium concentrations in the ambient air were estimated to range from 0.01 to 0.1 $\mu g/m^3$ at this distance from the factory. Occasionally, occupational exposure to beryllium has resulted increased mortality due to heart disease. A genetic predisposition for a human leukocyte antigen (HLA) class II may make some individuals more susceptible to chronic beryllium

disease. Other factors that may increase susceptibility to beryllium include lowered adrenal or liver function.

Dermal Exposure
Skin lesions have been reported in a few individuals occupationally exposed to beryllium. Skin ulceration occurred only if the skin had been accidentally cut.

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for beryllium is 2E-3 mg/kg/day based on a benchmark dose (BMD_{10}) of 0.46 mg/kg/day from a dog dietary study (US EPA, 2004). The BMD_{10} is the dose at the 95% CL of the dose-response model that corresponds to a 10% increase in effects relative to the control. The critical effect was small intestinal lesions. An uncertainty factor of 300 was applied to the RfD; including a factor of 10 was applied for interspecies extrapolation, 10 to account for intraspecies variation, and 3 for database deficiencies (US EPA, 2004). Oral LOAEL and NOAEL values have not been established for beryllium and overall confidence in the RfD value is low to medium.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for beryllium is 2E-2 $\mu g/m^3$ (2E-5 mg/m^3) based on a LOAEL of 0.55 $\mu g/m^3$ which caused beryllium sensitization of the immune system and progression to chronic beryllium disease in one of two principle human occupational studies (US EPA, 2004). Chronic beryllium disease is characterized by chronic inflammatory lung lesions associated with inhalation exposure to beryllium. A total uncertainty factor of 10 is applied to the RfC. The uncertainty factor is composed of a factor of 1 which accounts for the variability of human sensitivity to beryllium, a factor of 1 to account for the less than chronic duration of the occupational study that derived the RfC, a factor of 3 to account for the sensitivity of the experimental end point (beryllium sensitivity), and a database factor of 3 to account for poor quality of exposure monitoring in the two principle exposure studies and other epidemiological studies found. Confidence in the inhalation RfC is reported as medium for the quality of the study, database and RfC number.

Carcinogenic Effects
Several epidemiological studies show an increase incidence of lung cancer deaths amongst workers employed at beryllium factories (ATSDR, 2000). However, historical exposure levels were not reported so no correlation could be drawn between the incidence of lung cancer deaths and beryllium exposure.

The US EPA classifies inhaled beryllium and beryllium compounds as Class B1 - probable human carcinogen based on limited evidence for humans but sufficient data for animals (US EPA, 2004). The US EPA also indicates there are no studies on the potential carcinogenicity of ingested beryllium for humans and that the available animal studies do

not indicate that adverse effects exist (US EPA, 2004). The United States National Toxicology Program classifies beryllium and compounds as being reasonably anticipated carcinogens (NTP, 1994).

Carcinogenic Risk from Oral Exposure
The database for oral exposure to beryllium is considered inadequate, and an oral slope factor has not been determined (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An air unit risk of 2.4E-3 $(\mu g/m^3)^{-1}$ has been assigned based on the occurrence of lung cancer in an occupational inhalation exposure study on males (US EPA, 2004).

Summary

Oral Chronic RfD	2E-3 mg/kg/day	small intestinal lesions	US EPA, 2004
Inhalation RfC	2E-5 mg/m^3	sensitization, CBD*	US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Unit Risk	2.4E-3 $(\mu g/m^3)^{-1}$	lung cancer	US EPA, 2004

* CBD refers to chronic beryllium disease

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2000. Toxicological Profile for Beryllium.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Beryllium. URL: http://www.epa.gov/iris/

BETA-HEXACHLOROCYCLOHEXANE (b-HCH)

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The Beta-hexachlorocyclohexane (β-HCH) isomer can be absorbed into the body via inhalation, oral or dermal application. In general, all HCH isomers and their metabolic products can be temporarily stored in body fat, breast milk and semen (ATSDR, 2003). Of the HCH isomers, ß-HCH leaves the body the most slowly with excretion in the urine, feces and expired air. HCH is metabolized primarily by hepatic enzymes. Metabolites include various chlorophenols, some of which have toxic properties. The average absorption in rats following oral administration in feed for ß-HCH was approximately 90%. The distribution pattern for ß-HCH was found to be in the following order: fat > kidney > lungs > liver >muscle > heart > spleen > brain > blood (ATSDR, 2003). Accumulation of ß-HCH has been shown to increase approximately linearly with time of exposure. In comparison to other isomers, greater accumulation of ß-HCH is expected in tissues as ß-HCH is metabolized more slowly.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Rats fed ß-HCH have become comatose, with injury to the ovaries and testes also being reported. Once absorbed, HCH isomers are metabolized; some of these metabolites may be responsible for toxicity. Long-term oral administration of ß–HCH to laboratory rodents has been reported to result in liver cancer, and hypertrophied liver cells were reported in mice fed 45 mg/kg/day ß-HCH for 24 weeks and hepatomegaly was reported in mice exposed to 90 mg/kg/day in the diet for 50 weeks (ATSDR, 2003). Fatty chronic degeneration and necrosis in the liver of mice exposed to low doses of ß-HCH and hypertrophy and liver cancer in mice fed 34 mg/kg/day for 26 months were also reported. Significantly elevated excretion of glucose in urine, creatine and urea as well as hypertrophy and degeneration of the renal tubular epithelia in rats exposed to ß -HCH for up to 2 weeks was observed. Significant increases in kidney weights in female rats exposed to ß-HCH for 13 weeks have also been recorded. Neurological effects (e.g., ataxia, delay in tail nerve conduction velocity) have been reported in rats exposed to ß -HCH.

Acute oral exposure studies to β-HCH in mice found LOAELs to range from 57 mg/kg/day (ataxia) to 190 mg/kg/day (lateral recumbancy) (ATSDR, 2003). Chronic oral exposure studies using body weight endpoints to β-HCH in rats found NOAELs ranging

from 0.8 to 56 mg/kg/day. LOAELs for chronic oral exposure in rats ranged from 0.8 to 64 mg/kg/day based on hepatic endpoints.

Inhalation Exposure
In humans, the effects of breathing toxic levels of ß-HCH include blood disorders, dizziness, headaches, seizures, changes in sex hormone levels and occaisonally death. These effects have occurred in workers exposed to HCH vapors (including unspecified isomers) during pesticide manufacturing. Cardiovascular effects have been reported in humans exposed to HCH, and electrocardiogram abnormalities have been reported in 15% of 45 factory workers involved in the production of technical-grade HCH (unfortunately exposure concentrations were not reported, and simultaneous dermal exposure may have occurred).

Dermal Exposure
Reproductive effects in rats upon dermal exposure of β-HCH include atrophy of the ovaries and testes, fetal deaths, degeneration of the seminiferous tubules, and disruption of spermatogenesis. In addition, β-HCH mobilized from fat during fasting in rats produced estrogenic effects and stimulated growth of the uteri in ovariectomized mice. Genotoxic effects include chromosomal aberrations, and ß-HCH has been shown to induce liver carcinogens in rats and mice.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD is not available for β-HCH at this time (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC is not available for β-HCH at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified β-HCH as Class C – possible human carcinogen on the basis of several animal studies revealing increases in benign liver tumors and neoplasms in mice fed 200-600 ppm of β-HCH (US EPA, 2004). Human data are inadequate, with only one case report of a Japanese sanitation employee with acute leukemia associated with occupational exposure to HCH and DDT (US EPA, 2004). The US Department of Health and Human Services (DHHS) has determined that HCH (all isomers) may reasonably be anticipated to cause cancer in humans (ATSDR, 2003).

Carcinogenic Risk from Oral Exposure
The oral slope factor for ingested ß-HCH is 1.8 $(mg/kg/day)^{-1}$ based on the incidence of hepatic nodules and hepatocellular carcinomas observed in male mice administered ß-HCH at a single dose level of 200 ppm for 110 weeks in the diet (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure

An inhalation unit risk estimate of 5.3E-4 $(\mu g/m^3)^{-1}$ was derived for ß-HCH from the oral exposure data (US EPA, 2004).

Summary

Oral Chronic RfD	not available at this time		US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	1.8 $(mg/kg/day)^{-1}$	liver cancer	US EPA, 2004
Inhalation Unit Risk	5.3E-4 $(\mu g/m^3)^{-1}$	liver cancer	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2003. Toxicological Profile for β-hexachlorocyclohexane.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for beta-hexachlorocyclohexane. URL: http://www.epa.gov/iris/

BIS(2-ETHYLHEXYL)PHTHALATE (BEHP) OR DI(2-ETHYLHEXYL)PHTHALATE

Pharmacokinetics

Oral Exposure
About 20-25% of orally-administered bis(2-ethylhexy)phthalate (BEHP) and its metabolites are absorbed via the gastrointestinal tract in humans (ATSDR, 2002). Animal studies show that BEHP is hydrolyzed in the small intestine to mono(2-ethylhexyl)phthalate (MEHP) and 2-ethyhexanol, which are subsequently absorbed. Unhydrolyzed BEHP may also be absorbed in animal systems at high concentrations. Hydrolytic cleavage of BEHP is caused by esterases located throughout the body, with the highest levels occurring in the pancreas. MEHP undergoes further metabolism via oxidative reactions to produce 30 or more metabolites. Some of these additional metabolites can be conjugated with glucoronic acid for excretion in urine. In humans exposed to BEHP orally, approximately 65% of BEHP metabolites are excreted in urine as glucuronide condjugates (ATSDR, 2002). Unmetabolized BEHP may be excreted via the feces in humans. Data are not available regarding fecal excretion of BEHP in humans, however, it has been observed to be a significant pathway in animal studies.

Inhalation Exposure
Human data are not available for inhalation absorption, however it is expected that absorption will occur in the respiratory system (ATSDR, 2002). Limited human autopsy data are available and show that BEHP is present in fat and kidney tissues (ATSDR, 2002).

Dermal Exposure
Trace amounts of BEHP can also be absorbed through the skin (ATSDR, 2002).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
The toxicity of BEHP has been well studied in animals; however, human data are limited. Animal studies show that the primary effects of BEHP are hepatotoxicity, liver cancer and reproductive and developmental effects. Oral toxicity studies in humans are limited to a single case where two people ingested a large dose of BEHP and suffered gastrointestinal effects such as abdominal pain and diarrhea (ATSDR, 2002). Rodent studies show that BEHP has low acute toxicity and that young rodents may be more susceptible to effects than adult rodents (ATSDR, 2002). The rodent studies also indicate that the liver and testes are the major target organs of BEHP, when consumed orally (ATSDR, 2002). Non-human primates are much less sensitive to the hepatic and reproductive effects of BEHP than rodents (ATSDR, 2002). Female rodents who were chronically exposed to BEHP orally suffered from reproductive effects. BEHP is also

fetotoxic and teratogenic in rodents. The current weight-of-evidence indicates that BEHP is not genotoxic.

Inhalation and Dermal Exposure

Data are also limited regarding potential health effects resulting from inhalation or dermal exposure to BEHP in humans or animals. One study indicates the presence of lung disorders in pre-term children who had received respiratory support via PVC tubing. Although the health of these children was comprised due to the fact that they were pre-term, it is thought likely that the lung disorders were associated with BEHP released from the PVC tubing (ATSDR, 2002). Inhalation studies in rodents did not demonstrate reproductive or developmental toxicity. A dermal study did not find any skin irritation or sensitization in humans or rabbits (ATSDR, 2002).

Reference Dose for Chronic Oral Exposure (RfD)

The US EPA has developed an RfD for BEHP of 0.02 mg/kg/day based on a study that found increased liver weight in guinea pigs exposed to BEHP (US EPA, 2004). Groups of guinea pigs were fed a diet containing 0, 19 and 64 mg/kg/day BEHP for one year. Assessment endpoints included mortality, body weight, kidney weight, and gross pathology and histopathology of several organs. No treatment-related effects were observed in any of the assessment endpoints other than relative liver weight. Statistically significant increases in relative liver weights were observed in the females from both the 19 and 64 mg/kg/day BEHP exposed groups. A parallel BEHP study was conducted with rats. Groups of rat were exposed to 20, 60 and 195 mg/kg/day BEHP for a period of two years. Rats who received the 195 mg/kg/day dose demonstrated decreased growth and increased kidney and liver weights; effects were not observed at lower BEHP doses. The guinea pigs were found to be more sensitive to BEHP than rats and a LOAEL was determined to be 19 mg/kg/day. A NOEAL could not be determined from this study.

An uncertainty factor of 1000 was applied to the NOAEL to derive an RfD of 0.02 mg/kg/day. The uncertainty factor consists of: a factor of 10 to account for interspecies extrapolation; a factor of 10 to account for sensitive subpopulations; a factor of 10 to account for the use of a subchronic study to develop a chronic RfD; and the use of a LOAEL to set an RfD (US EPA, 2004). The US EPA indicates that confidence in the RfD is medium because, although the study was well designed, only two test concentrations were included. The database confidence is also medium because two species were included in the chronic animal bioassays. As confidence in both the primary study and the database are medium, confidence in the RfD is also medium.

Reference Concentration for Chronic Inhalation Exposure (RfC)

An RfC is not available for BEHP at this time (US EPA, 2004).

Carcinogenic Effects

BEHP is classified as a Class B2 – probable human carcinogen. Although human data are inadequate to make a carcinogenic determination, studies show that BEHP produces

dose-related increase in liver tumors in rodents (US EPA, 2004). There is sufficient indication from animal bioassay data that BEHP will likely cause cancer in humans.

Carcinogenic Risk from Oral Exposure
The US EPA (2004) derived a slope factor of 0.014 $(mg/kg/day)^{-1}$ for BEHP based on increased incidence of hepatocellular carcinomas and adenomas in mice. Groups of rats and mice were fed diets containing BEHP. Rats were exposed to BEHP doses of 0, 6000 or 12,000 ppm, while mice were exposed to 0, 3000, or 6,000 ppm for 103 weeks. Animals were examined upon death or at 105 weeks. None of the rats or mice demonstrated clinical signs of toxicity (US EPA, 2004). Female rats and all mice demonstrated a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas. Male rats exposed to the highest dose of BEHP also experienced an increase in combined neoplastic nodules and hepatocellular carcinomas. A standard food consumption rate of 13% mouse body weight was used in dose conversion to account for feed spillage and waste, rather than relying on measured food intake. The US EPA indicates that an adequate number of animals were tested and a statistically significant increase in the incidence of liver tumors was noted in both male and female animals. Feed scattering was identified as a potential source of variability in this study.

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for BEHP at this time (US EPA, 2004).

Summary

Oral Chronic RfD	0.02 mg/kg/day	increased liver weight	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	$0.014(mg/kg/day)^{-1}$	liver tumors	US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2002. Toxicological Profile for Di(2-ethylhexyl)phthalate.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Di(2-ethylhexyl)phthalate. URL: http://www.epa.gov/iris/

BROMODICHLOROMETHANE (BDCM)

Pharmacokinetics

Oral Exposure

There have been few studies on the pharmacokinetics of bromodichloromethane (BDCM) in experimental animals, and no studies have been found on human exposure (ATSDR, 1989). Oral exposure is the only pathway that has been characterized from a pharmacokinetic perspective. Absorption of BDCM though oral intake was studied in female monkeys, and mice and rats. The monkey study administered radioactive BDCM through gavage to females, and found that 2% of the administered radioactivity was excreted in feces, indicating almost complete absorption by the gastrointestinal tract. A similar study of mice also found that absorption was rapid and extensive, with 90% of the administered radioactivity excreted in urine or expired air. Lower absorption rates were found in a rat study, with only 60% of the administered dose excreted in air or urine. Another rat study found the distribution of BDCM from oral gavage exposure was slow; 3 hours after administration, 21.5% of the dose remained in the stomach and fat, muscle and liver cells contained between 1.8 to 2.8% of the dose. BDCM metabolism has not been characterized, although mice studies indicate CO_2 is the major end-product (81% of the administered dose). Rat studies found lower rates of CO_2 production (14%) in addition to the excretion of unaltered BDCM (42%). Oral intake studies on rats, mice and monkeys found the major route of excretion is through the lungs, as either unaltered BDCM or CO_2 and similar metabolites. Urine excretion is a minor route, accounting for 1.4% in rats, 2.2% in mice and 2 to 6% in monkeys. BDCM half-life in rats is approximately 1.5 hours, 2 hours in mice, and 4-6 hours in monkeys, indicating excretion is rapid and tissue accumulation is unlikely.

Inhalation and Dermal Exposure

No studies were found on the absorption, distribution and excretion of BDCM through inhalation or dermal exposure, although based on the results from studies with chemicals having similar molecular structures, it is possible that BDCM may be readily absorbed across the lungs and skin in humans and animals (ATSDR, 1989).

Toxicity

Non-Carcinogenic Effects

Oral Exposure

No studies have been found linking environmental levels of BDCM with toxicity in humans, although oral exposure studies in animals have found liver injury (in acute tests with doses of 1,250 mg/kg or higher), kidney injury (at similar doses), and increased incidences of fetal abnormalities in rats (at doses of 50 to 200 mg/kg/day at days 6 to 15 of gestation). Pretreatment of rats with oral doses of acetone was shown to significantly

increase the toxicity of BDCM to the liver and kidneys (ATSDR, 1989). Synergistic toxic effects also occur with acetone and carbon tetrachloride (CCl_4), another halogenated methane, which suggests BDCM and carbon tetrachloride have similar mechanisms of toxicity.

Oral uptake of BDCM has been studied with experimental animals (ATSDR, 1989). Acute oral LD_{50} values in rodents range from 400 to 1000 mg/kg. Male rats and mice are slightly more susceptible than females. NOAELs from gavage intake studies ranged from 11.6 mg/kg/day in mice to as high as 396 mg/kg/day in rats. LOAELs from gavage intake studies ranged from 11.6 mg/kg/day in mice (causing neurological damage) to as high as 1500 mg/kg/day in rats (also causing neurological damage) (ATSDR, 1989).

Inhalation and Dermal Exposure
Toxicity of BDCM through inhalation or dermal exposure has not been characterized.

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for BDCM is 0.02 mg/kg/day based on a LOAEL of 17.9 mg/kg/day from a chronic mouse gavage study (US EPA, 2004). The LOAEL was based on renal cell enlargement in male mice, and was considered a minimal effect based on the absence of impairment of kidney function. The total uncertainty factor applied to the LOAEL was 1000; including a factor of 100 for extrapolation to humans and protection of sensitive subpopulations, and an additional factor of 10 because the RfD was based on a LOAEL, and reproduction studies were lacking. Confidence in the oral RfD is reported as medium for the quality of the study, database and RfD (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for BDCM is unavailable (US EPA, 2004)

Carcinogenic Effects
Bromodichloromethane is considered a Class B2 carcinogen – probable carcinogen. This classification is based on the inadequacy of human studies and sufficient data from mice and rat studies. Carcinogenic effects include increased incidences of kidney and large intestine tumors in male and female rats, kidney tumors in male mice and liver tumors in female mice (US EPA, 2004). Some studies indicate there may be an association between the consumption of chlorinated municipal drinking water and an increased risk of cancer in humans (ATSDR, 1989). This association has not been validated, as there are numerous other chemicals present in chlorinated municipal water (no studies have differentiated the effects of individual chemicals).

Carcinogenic Risk from Oral Exposure
The oral slope factor for BDCM is 0.062 $(mg/kg/day)^{-1}$ and is based on kidney tumors found in male mice following gavage administration (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation unit risk value is not available for BDCM (US EPA, 2004).

Summary

Oral chronic RfD	0.02 mg/kg/day	renal effects	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	0.062 $(mg/kg/day)^{-1}$	renal tumors	US EPA, 2004
Inhalation Unit Risk	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1989. Toxicological Profile for Bromodichloromethane.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Bromodichloromethane. URL: http://www.epa.gov/iris/

N-BUTYLBENZENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
No information was found on the pharmacokinetics of n-butylbenzene in humans or animals.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
No information was found on the toxicity of n-butylbenzene to humans or animals.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD is not available for n-butylbenzene on the US EPA IRIS website, but an RfD_o of 4E-2 mg/kg/day was listed on an April 2003 version of the US EPA Region 3 (this value has since been removed) (US EPA Region 3, 2003).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC was not found for n-butlbenzene.

Carcinogenic Effects
Carcinogenicity information was not found for n-butlbenzene.

Carcinogenic Risk from Oral Exposure
An oral slope factor was not found for n-butlbenzene (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor was not found for n-butlbenzene (US EPA, 2004).

Summary

Oral Chronic RfD	4E-2 mg/kg/day	US EPA Region 3, 2003
Inhalation RfC	not found	US EPA, 2004
Oral Slope Factor	not found	US EPA, 2004
Inhalation Slope Factor	not found	US EPA, 2004

References

United States Environmental Protection Agency (US EPA) Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 4/25/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS). URL: http://www.epa.gov/iris/

CADMIUM

Pharmacokinetics

Oral and Inhalation Exposure
The major site of cadmium absorption in humans following inhalation is the alveoli of the lung, while the majority of ingested cadmium tends to pass through the gastrointestinal tract without being absorbed and is excreted in the feces (ATSDR, 1999). Absorbed cadmium from the lungs and gastrointestinal tract tends to be excreted very slowly and is found equal proportions in the urine and feces (ATSDR, 1999). The two main target organs for cadmium are the kidney and liver. The half-life of cadmium in the human body is very long; an estimated half-life for cadmium in the kidney ranges from 6 to 38 years and the liver from 4 and 19 years (ATSDR, 1999). The placenta may act as a partial barrier to fetal cadmium exposure (ATSDR, 1999). Cadmium is not metabolized, but is bound to proteins and other molecules; in particular, cadmium binds to albumin (a protein) in the bloodstream and is transported to the liver (ATSDR, 1999). Once cadmium enters the liver it becomes bound to another protein called metallothionein and is re-released to the bloodstream. The metallothionein-bound cadmium is then filtered by the kidney glomerulus and is reabsorbed by the proximal tubule cells. Lysozymes (strong enzymes) degrade the cadmium-metallothionein complex and allow free cadmium to be released in the kidney. The free cadmium initiates the synthesis of metallothionein in the proximal tubule cells and can also cause excessive damage to the kidneys.

Dermal Exposure
There is currently not enough information to determine the potential absorption of cadmium via the dermal route of exposure (ATSDR, 1999). Based on the limited information it appears that very little cadmium is absorbed through the skin

Toxicity

Non-Carcinogenic Effects
Oral Exposure
High acute oral doses of cadmium (0.07 mg/kg) may cause gastrointestinal effects such as nausea, vomiting, and abdominal pain (Nordberg et al, 1973 in ATSDR, 1999). Anemia can result from oral or inhaled cadmium, and if transported to the gut, cadmium will cause reduced iron absorption. However, in populations with adequate dietary intake of iron, it is likely that cadmium-induced anemia will not be a problem, as the increased intake will compensate for decreased absorption (ATSDR, 1999). Chronic cadmium exposure coupled with poor nutrition can lead to changes in the way which the kidney metabolizes vitamin D, causing a painful bone diseases such as osteomalacia and osteoporosis (ATSDR, 1999). Cadmium causes kidney damage, particularly to the renal

tubules in the early stages and as the disease progresses or dose increases, glomerular damage is also observed (ATSDR, 1999). There are limited data to suggest that cadmium exposures in pregnant women may result in decreased birth weight in their babies (ATSDR, 1999). Populations that may be unusually susceptible to cadmium exposure are those with a genetic predisposition to lower inducibility of metallothionein, the enzyme that sequesters cadmium. Increased absorption of cadmium from the gastrointestinal tract may result in individuals with depleted levels of calcium or iron resulting from dietary deficiencies (ATSDR, 1999). Infants and children may have increased uptake of cadmium via the gastrointestinal tract and higher concentrations of cadmium in the bone.

Inhalation Exposure
Inhalation of cadmium at 5 mg/m^3 has resulted in pulmonary edema, tracheobronchitis and pneumonitis in humans (ATSDR, 1999).

Dermal Exposure
Cadmium appears to have a relatively low dermal toxicity based on occupational studies where workers who were exposed to high levels of cadmium dust did not report any dermal effects. In addition, cadmium does not appear to cause sensitization by repeated dermal contact (ATSDR, 1999).

Reference Dose for Chronic Oral Exposure (RfD)
The US EPA has developed oral reference doses for cadmium for food and water. The oral reference dose for food is 1E-3 mg/kg/day and for water is 5E-4 mg/kg/day (US EPA, 2004). The highest cadmium level in the human kidney that does not produce proteinuria has been determined to be 200 µg/g of wet kidney cortex. A toxicokinetic model was used to determine the level of chronic oral exposure that would result in a cadmium kidney concentration of 200 µg /g of wet kidney cortex. The toxicokinetic model assumes that 0.01% of the body cadmium kidney burden is eliminated daily and that absorption of cadmium from food and water are 2.5% and 5%, respectively. A NOAEL for chronic cadmium exposure via water and food was determined to be 0.005 and 0.01 mg/kg/day, respectively. An uncertainty factor of 10 to account for human variability was applied to the NOAELs to develop the reference doses for water and food.

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for cadmium is not available at this time (US EPA, 2004). A provisional chronic inhalation reference dose of 5.7E-5 mg/kg/day is available from US EPA NCEA (US EPA Region 3, 2003).

Carcinogenic Effects
Epidemiological studies demonstrate increased incidence of lung cancer in workers exposed to cadmium via the inhalation route, however, the studies did not control for factors such as smoking and simultaneous exposures to other metals so the causal

relationship is somewhat controversial. Oral exposure to cadmium has not been associated with cancer in humans, however available studies are inadequate to assess carcinogenicity. The US EPA has classified cadmium as a Class B2 – probable human carcinogen based on limited human and sufficient animal data (US EPA, 2004)

Carcinogenic Risk from Oral Exposure
An oral slope factor for cadmium is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
A quantitative assessment of carcinogenic risk from inhalation exposure was conducted, and the air unit risk was calculated to be 1.8E-3 $(\mu g/m^3)^{-1}$ (US EPA, 2004).

Summary

Oral chronic RfD	1E-3 mg/kg/day (food)	proteinuria	US EPA, 2004
Oral chronic RfD	5E-4 mg/kg/day (water)	proteinuria	US EPA, 2004
Inhalation RfD	5.7E-5 mg/kg/day	US EPA Region 3, 2003	
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Unit Risk	1.8E-3 $(\mu g/m^3)^{-1}$	lung cancer	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Toxicological Profile for Cadmium.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Cadmium. URL: http://www.epa.gov/iris/

US EPA Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

CHLOROFORM

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The adsorption, distribution, metabolism and excretion pathways of chloroform are well known based on studies with experimental animals. In general, chloroform is easily absorbed into the blood stream following inhalation exposure, with peak levels occurring 5 to 6 minutes following oral uptake (dermal uptake is also possible) (ATSDR, 1997). Chloroform is then distributed to adipose tissues, brain, liver, kidneys, blood, adrenal and embryonic neural tissue. In humans, approximately 50% of chloroform is eventually metabolized to CO_2 with an intermediate metabolite phosgene formed in the liver (the main site of metabolism). Chloroform is excreted in small amounts in the urine or feces in the unaltered form or as CO_2 following pulmonary desorption.

Toxicity

Non-Carcinogenic Effects
Oral and Inhalation Exposure
Chloroform can affect the central nervous system, liver, and kidneys after inhalation or oral exposure from the air or water (ATSDR, 1997). Acute inhalation exposure causes fatigue, dizziness and headache, while chronic exposure can cause liver and kidney damage.

Chloroform oral uptake studies with experimental animals found NOAELs ranging from 0.96 mg/kg/day in a chronic human study (renal and hepatic endpoints) to 765 mg/kg/day (administered once) in female mice (immune system endpoints). The oral intake LOAEL values range from 15 mg/kg/day in beagles (causing increased liver enzyme activity) to 2180 mg/kg/day in female rats (an LD_{50}) and up to 2410 mg/kg/day in a male human (causing a arrhythmia, jaundice and toxic hepatitis, oliguria and deep coma).

Inhalation uptake studies on experimental animals found NOAELs ranging from 1.99 ppm (9.7 mg/m^3) over 13 weeks (7 days per week and 6 days per hour) in male mice (focusing on renal effects) to 2500 ppm (12,200 mg/m^3) over 0.5 to 2 hours in mice (focusing on the neurological system) (ATSDR, 1997). Chloroform LOAELs from inhalation uptake studies range from 10 ppm (48.8 mg/m^3) for 7 days, 6 hours per day in female mice (causing an increased number of S-phase nuclei and mild, transient, proliferative responses and bone thickening in the periosteum and posterior ventral areas in the respiratory system) to 9770 ppm (47,677 mg/m^3) over 4 hours in female rats (an LC_{50} value) and up to 22,500 ppm (109,800 mg/m^3) over 0.5 to 2 hours in humans

(causing vomiting, respiratory changes, cardiac arrhythmia and bradycardia, and narcosis).

Dermal Exposure
Dermal application of 0.01 mL chloroform for 24 hours to rabbits caused slight skin irritation. Application of 1,000 mg/kg resulted in skin necrosis and weight loss in rabbits (ATSDR 1997).

Reference Dose for Chronic Oral Exposure (RfD)
The Oral RfD for chloroform is 0.01 mg/kg/day based on a LOAEL of 15 mg/kg/day (converted to 12.9 mg/kg/day based on continuous exposure) from a chronic exposure study on dogs (US EPA, 2004). The LOAEL is based on moderate to marked fatty cyst formation in the liver and elevated liver enzymes. The total uncertainty factor is 1000 based on a UF of 10 to account for interspecies extrapolation, a factor of 10 for the protection of sensitive subpopulations and a third factor of 10 to account for the extrapolation of a LOAEL to a NOAEL. In this case a benchmark dose (BMD) approach was also used (resulting in the same RfD value), and is considered a preferable derivation for the RfD.

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for chloroform is unavailable at this time (US EPA, 2004).

Carcinogenic Effects
Chloroform is considered a Class B2 carcinogen – probable carcinogen. This classification is based on sufficient animal test evidence (US EPA, 2004). Inconclusive evidence has been found linking cancer in humans with the consumption of chlorinated drinking water; confounding factors include the presence of numerous chlorination byproducts (ATSDR, 1997).

Carcinogenic Risk from Oral Exposure
An oral slope factor for chloroform carcinogenicity is not applicable, because available information shows the carcinogenic effects is secondary to another toxicity threshold (in this case cytotoxicity and regenerative hyperplasia). In this case, an RfD of 0.01 mg/kg/day is considered to be protective against the risk of cancer (US EPA, 2004). A provisional value from US EPA NCEA is 1.4E-2 mg/kg/day (US EPA Region 3, 2003).

Carcinogenic Risk from Inhalation Exposure
The inhalation unit risk value for chloroform is 2.3E-5 $(\mu g/m^3)^{-1}$ based on a gavage-administered dose on a female mouse causing liver cancer (US EPA, 2004).

Summary

Oral chronic RfD	0.01 mg/kg/day	liver damage	US EPA, 2004
Inhalation RfD	not available at this time		US EPA, 2004
Oral Slope Factor	1.4E-2 mg/kg/day		US EPA Region 3, 2003
Inhalation Unit Risk	2.3E-5 $(\mu g/m^3)^{-1}$	liver cancer	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological Profile for Chloroform.

United States Environmental Protection Agency (US EPA) Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Chloroform. URL: http://www.epa.gov/iris/

CHROMIUM (III AND VI)

Pharmacokinetics

Oral Exposure
The absorption of chromium following oral, inhalation or dermal exposure is dependent on two things: the valence state of chromium atom and what it is bound to (i.e., the ligand form) (ATSDR, 2000). Absorption of Cr(VI) is higher than Cr(III) because the chromate ion $(CrO_4)^{-2}$ can enter cells via facilitated diffusion through anion channels, while Cr(III) must be absorbed via passive diffusion or phagocytosis (ATSDR, 2000). Oral exposure studies have found absorption of Cr(III) in the highly insoluble form of chromic oxide is not detectable, the absorption of Cr(III) as dietary compounds is 0.5 to 2.0% following ingestion (ATSDR, 2000). Chromium is distributed to many organs; autopsy studies in the US have found the highest concentrations in the kidneys, liver, lungs, aorta, heart, pancreas and spleen (at birth), which tend to decrease with age. Animal studies have found similar distribution of chromium following oral exposure; as absorption following oral exposure is relatively low, the major excretion pathway via feces. A study of humans exposed to radiolabeled Cr(III) (as chromium chloride) and Cr(VI) (as sodium chromate) found 99.6 and 89.4%, respectively, in the feces six hours post-exposure, and 0.5 and 2.1% in the urine 24 hours post-exposure. Similar levels of fecal excretion have been found in rat and hamster studies.

Inhalation Exposure
Inhalation exposure studies have found chromium is absorbed through the lungs and gastrointestinal tract (following mucocilary particle clearance from the lungs). In most studies, Cr(VI) compounds were more readily absorbed from the lungs than Cr(III), and it was noted that the size and solubility of the particle, as well as the activity of alveolar macrophages affected the relative rates of uptake. Because chromium has a high boiling point, most chromium in the air is in the form of particle-bound chromium or chromium dissolved in droplets, not gaseous chromium. Following inhalation exposure in humans, chromium was distributed to the hiliar lymph nodes, lung, spleen, liver, kidneys and heart from occupational exposure (ATSDR, 2000). Chromium may also be passed to fetuses through the placenta and infants through breast milk. Similar organ targets have been found in animal studies. Workers exposed to Cr(VI) compounds have been shown to have higher urinary concentrations of chromium compared to workers exposed to Cr(III).

Dermal Exposure
Dermal exposure studies have shown chromium is also absorbed trans-dermally, with the rate of transfer affected by the integrity of the skin (ATSDR, 2000). System toxicity has been observed in humans following dermal exposure to a mixture of chromium compounds. Fourteen (14) days following exposure to a salve containing potassium

chromate to treat scabies, chromium was found in the blood (2 to 5 mg/100 mL), urine (8 mg/L), feces (0.61 mg/100 g) and stomach contents (0.63 mg/100 mL). A pre-existing case of scabies or necrosis causing broken skin may have facilitated absorption. Dermal absorption by animals has also been noted in guinea pigs as radiolabeling studies have found Cr(III and VI) distribution to the blood, spleen, bone marrow, lymph glands, urine and kidneys, with greater absorption of the (VI) form. Information on the excretion of chromium following dermal exposure is limited; the human study with the application of a potassium chromate salve found 8 mg/L chromium in the urine and 0.61 mg/100 g in the feces 14-days after exposure.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Accidental or intentional ingestion of chromium compounds is known to cause death in humans; autopsies have revealed effects including edema, severe bronchitis, acute bronchopneumonia, early hypoxic changes in the myocardium, liver congestion and necrosis of the liver, renal tubules and gastrointestinal tract (ATSDR, 2000). Gastrointestinal effects from ingestion of 7.5 mg/kg Cr(VI) included abdominal pain and vomiting (prior to death). Hematological effects from oral uptake in humans include decreased hemoglobin content and hematocrit, and an increase in total white blood cell counts, reticulocyte counts and plasma hemoglobin 4 days after ingestion of potassium dichromate (Cr(VI)). Liver damage following Cr(VI) ingestion included jaundice, increased bilirubin and increased serum lactic dehydrogenase with kidney damage including acute renal failure, with proteinuria and hematuria. A rat study found oral exposure via gavage of 13.5 mg/kg/day Cr(VI) as potassium chromate for 20 days resulted in increased accumulations of lipids, relocalization of liver enzymes and an increased accumulation of lipids, accumulated triglycerides and phospholipids in different regions of the kidneys. Significant decreases in body weight gain were noted in a rat study with exposure to Cr(VI) 42 mg/kg/day for 12 weeks (causing a 19% decrease) and 6 mg/kg/day for 12 weeks (causing a 10% decrease). Reproductive and developmental effects have also been reported in animal oral exposure studies.

Chromium (III) oral exposure studies found NOAELs ranging from 9 mg/kg/day in rats (administered daily in feed over 20 weeks) to 2040 mg/kg/day in rats (administered in feed for 2 years, 5 days/week). Oral exposure LOAELs for chromium (III) ranged from 5 mg/kg/day (administered in water over 12 weeks) in male and female rats (cauaing decreased body weight) to 2365 mg/kg/day following a single dose via gavage with water in rats (causing death in 50% of the population) (ATSDR, 2000).

Chromium (VI) oral exposure studies found NOAELs ranging from 1.1 mg/kg/day in male mice (administered over 9 weeks in feed) to 53.2 mg/kg/day in female mice (administered in water over 9 days, for gestational days 6 to 14). Oral LOAELs for

chromium (VI) ranged from 0.036 mg/kg/day in humans (administered once, causing dermatitis) to 811 mg/kg/day in male rats (administered once, corresponding to an LD_{50} value) (ATSDR, 2000).

Inhalation Exposure

Studies of the toxicity of chromium following inhalation exposure have found the respiratory tract is a major target in humans; dyspnea, cough, and wheezing have occurred following exposure to elevated chromium concentrations (ATSDR, 2000). Intermediate and chronic exposure has also been shown to increase the risk of non-cancer respiratory disease causing death. Regular occupational exposure has been found to cause the following gastrointestinal effects: stomach pain, duodenal ulcer, gastritis, stomach cramping and frequent indigestion (average exposure duration was 7.5 years, and mean concentrations were 0.004 mg/m^3 Cr(VI)). Liver effects include derangement of cells in the liver, necrosis, lymphocytic and histiocytic infiltration and Kupffer cell increases, and kidney damage is indicated by the presence of white blood cell and red blood cell casts in the urine.

Inhalation studies on chromium (III) found NOAELs ranging from 0.022 mg/m^3 in humans (from a mixture of Cr (III), (VI) and chromite, over an 8 year period) to 1.99 mg/m^3 (also in humans, from a mixture of Cr (III) and (VI)) from chronic exposure (ATSDR, 2000). Inhalation LOAELs for chromium (III) ranged from 0.04 mg/m^3 in humans over 1 to 49 years of occupational exposure (corresponding to a cancer effect level for lung cancer) to as high as 0.9 mg/m^3 over 30 minutes of exposure in hamsters (causing increased acid phosphatase activity in lung tissue) (ATSDR, 2000).

Inhalation studies on chromium (VI) found NOAELs ranging from 0.022 mg/m^3 in humans (from a mixture of Cr (III), (VI) and chromite, over an 8 year period) to 1.99 mg/m^3 (also in humans, from a mixture of Cr (VI) and (III)) from chronic exposure (duration not specified) (ATSDR, 2000). Inhalation LOAELs for chromium (VI) ranged from 0.002 mg/m^3 following 0.2 to 23.6 years of occupational exposure in humans (causing nasal mucosa atrophy and mild decreased lung function) to as high as 137 mg/m^3 in male rats following 4 hours exposure (corresponding to an LC_{50} value) (ATSDR, 2000).

Dermal Exposure

Absorption following dermal exposure to Cr(VI) is enhanced by the caustic nature of many Cr(VI) compounds, and often leads to burns and systemic toxicity (ATSDR, 2000). Occupational studies on dermal exposure have found direct contact of chromium dust and mists leads to nose and throat irritation. A study where individuals applied a salve containing potassium chromate (to treat scabies) found cardiovascular effects including weak, thready and markedly dicrotic pulse, acute nephritis, and severe leukocytosis and symptoms of hemolytic anemia (ATSDR, 2000). Contact dermatitis in sensitive

individuals and other skin irritations include skin burns, blisters and skin ulcers. In a study of chromate workers in the US, 50% of the study group had skin ulcers or scars. Animal studies have found similar dermal effects following dermal exposure; at an application of 42 to 55 mg/kg Cr(VI), rabbits showed effects including skin inflammation, edema and necrosis.

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for Cr(III) as insoluble salts is 1.5 mg/kg/day from a chronic rat feeding study (unspecified effects) with a NOAEL of 5% Cr_2O_3 administered in the diet for 5 days/week and 600 feedings (adjusted to 1,468 mg/kg/day) (US EPA, 2004a). The total uncertainty factor was 100 including a factor of 10 for interspecies conversion and an additional factor of 10 to protect sensitive sub-populations. A modifying factor of 10 was used to account for database deficiencies. Confidence is low for the quality of the study, database and RfD value. Confidence is low due to the lack of (a) detail on study methodology and results, (b) high-dose supporting data and (c) an observed effect level at any dose (i.e., the NOAEL was assigned to the highest dose tested).

The RfD for Cr(VI) is 3E-3 mg/kg/day based on a 1-year drinking water study in rats. The NOAEL was 25 mg/L K_2CrO_4 (adjusted to 2.5 mg/kg/day) (US EPA, 2004b). The total uncertainty factor was 300 consisting of a factor of 10 for interspecies conversion, a factor of 10 to protect sensitive sub-populations and an additional factor of 3 for the less-than-lifetime exposure duration of the principle study. Confidence in the oral RfD is reported as low due to the small number of test subjects used, small number of parameters measured and lack of toxic effect at the highest test dose. The confidence in the database is also low based on the low quality of supporting studies and lack of developmental toxicity characterization.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for Cr(III) as insoluble salts is not available at this time due to a lack of adequate test data (US EPA, 2004a).

The RfC for Cr(VI) is separated by form into chromic acid mists / dissolved aerosols and particulates. The RfC for Cr(VI) as chromic acid mists / dissolved aerosols is 8E-6 mg/m^3 based on a human sub-chronic occupational study (with a critical effect of nasal septum atrophy) (US EPA, 2004b). A NOAEL value was not determined, but the LOAEL was 2E-3 mg/m^3 (adjusted to 7.14 E-4 mg/m^3). The uncertainty factor for this RfC is 90, and the confidence in the study, database and RfC value is low based on uncertainties regarding exposure characterization and the role of direct contact on the critical effect (supporting studies are equally uncertain regarding this exposure characterization). The RfC for particulate Cr(VI) is 1E-4 mg/m^3 based on a BMD-analysis in a subchronic study in rats, with lactate dehydrogenase in the bronchioalveolar lavage fluid as the critical effect utilized. The BMD was 0.016 mg/m^3 (adjusted to 0.034 mg/m^3), and the uncertainty factor is 300. The confidence in the study and RfC value is medium based on

uncertainties regarding upper respiratory, reproductive and renal effects resulting from exposure to particulate Cr(VI).

Carcinogenic Effects

The US EPA has classified chromium (III) as a group D carcinogen – not classifiable as to human carcinogenity, due to a lack of human data and inadequate data from animal studies (US EPA, 2004a).

Chromium (VI) is classified as a Group A carcinogen – known human carcinogen (by the inhalation exposure route) (US EPA, 2004b). Lung cancer has been found in human studies, with consistent data from animal studies; tumor types include intramuscular njection site tumors in mice and rats, intrapleural implant site tumors in rats, intrabronchial implantation site tumors in rats and subcutaneous injection site sarcomas in rats (US EPA, 2004b). The carcinogenicity of the oral exposure route cannot be determined, and as a result, Cr(VI) is classified as Group D – not classifiable as to human carcinogenicity for oral exposure.

Carcinogenic Risk from Oral Exposure

An oral slope factor is not available for Cr(III) as insoluble salts at this time (US EPA, 2004a).

An oral slope factor is not available for Cr(VI) at this time (US EPA, 2004b).

Carcinogenic Risk from Inhalation Exposure

An inhalation slope factor is not available for Cr(III) as insoluble salts at this time (US EPA, 2004a)

There has not been an inhalation slope factor assigned for Cr(VI), although the air unit risk is 1.2E-2 $(\mu g/m^3)^{-1}$ based on the occurrence of lung cancer from an occupational study in humans (US EPA, 2004b).

Summary

Cr(III)			
Oral Chronic RfD	1.5 mg/kg/day	NOAEL	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004
Cr(VI)			
Oral Chronic RfD	0.003 mg/kg/day	NOAEL	US EPA, 2004
Inhalation RfC (a)	8E-6 mg/m^3	nasal damage	US EPA, 2004
Inhalation RfC (b)	1E-4 mg/m^3	lung effects	US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Unit Risk	1.2E-2 $(\mu g/m^3)^{-1}$	lung cancer	US EPA, 2004

Note: there are two RfC values for Cr(VI); (a) refers to chromic acid mists and aerosols, (b) refers to particulates. The RfC for particulates was used in this risk assessment.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2000. Toxicological Profile for Chromium.

United States Environmental Protection Agency (US EPA). 2004a. Integrated Risk Information System (IRIS) Summary for Chromium (III), insoluble salts. URL: http://www.epa.gov/iris/

US EPA. 2004b. Integrated Risk Information System (IRIS) Summary for Chromium (VI). URL: http://www.epa.gov/iris/

US EPA. 1998a. Toxicological Review of Trivalent Chromium in Support of Summary Information on the Integrated Risk Information Risk System (IRIS).

US EPA. 1998b. Toxicological Review of Hexavalent Chromium in Support of Summary Information on the Integrated Risk Information Risk System (IRIS).

CHRYSENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The pharmacokinetics of chrysene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
The toxicity of chrysene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD for chrysene is not available at this time (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for chrysene is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified chrysene as Class B2 – probable human carcinogen (US EPA, 2004). Although no human data were available, there is sufficient indication from animal bioassay data that chrysene will likely cause cancer in humans. Carcinomas and malignant lymphoma were observed in mice administered chrysene via intraperitoneal injection. Skin carcinomas resulted from dermal exposure to chrysene in mice studies (US EPA, 2004). Gavage exposure of chrysene resulted in chromosomal abnormalities in hamster and mouse germ cells. Bacterial studies show that chrysene is mutagenic. Chrysene can also cause transformations in mammalian cell cultures (US EPA, 2004). Quantitative estimates of slope factors or unit risk values are not available at this time (US EPA, 2004). Carcinogenic assessment of chrysene was conducted using a toxic equivalency factor (TEF) approach. Some PAHs are assigned carcinogenicity relative to benzo(a)pyrene (see PAH toxicity profile for explanation).

Carcinogenic Risk from Oral Exposure
An oral slope factor for chrysene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for chrysene is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD	not available at this time	US EPA, 2004
Inhalation RfC	not available at this time	US EPA, 2004
Oral Slope Factor	not available at this time	US EPA, 2004
Inhalation Slope Factor	not available at this time	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Chrysene. URL: http://www.epa.gov/iris/

COBALT

Pharmacokinetics

Oral Exposure
Oral consumption of cobalt results in absorption by the gastrointestinal tract; absorption ranges from 18 to 97% in humans and is dependent upon the dose and form of cobalt as well as the nutritional status of the individuals exposed. Cobalt absorption tends to increase in subjects with iron deficiencies in their diet. Elimination in the feces is the primary excretion method for oral cobalt exposures.

Inhalation Exposure
Inhaled cobalt particles accumulate in the respiratory tract, and particle size determines whether accumulation occurs in the upper or lower respiratory tract. Larger particles (> 2 µm) tend to accumulate in the upper respiratory tract, while smaller particles are transferred to the lower respiratory system. From the lungs, cobalt particles either dissolve into the bloodstream or are transferred to the gastrointestinal tract by actions such as swallowing. Approximately 50% of the cobalt transferred to the gastrointestinal tract is actually absorbed and the rest is eliminated in the feces. About 50 % of the portion of the initial lung burden can remain up to 6 months after exposure (Foster et al, 1989 as cited in ATSDR, 1992).

Dermal Exposure
Human dermal exposure (hands only) to hard metal dust (~5–15% cobalt metal, 95–85% tungsten carbide) for 90 minutes showed an increase in urinary cobalt levels by an order of magnitude up to 60 hours after the exposure. The absorption of $2.2x10^{-5}$ mg ^{60}Co/kg as cobalt chloride through the intact or abraded skin of guinea pigs revealed absorption to be very limited through intact skin (<1%), while absorption through abraded skin was almost 80%. No studies were available regarding distribution in humans or animals after dermal exposure to cobalt. Excretion of cobalt in hamsters occurs primarily in the urine within 48 hours after a single dermal exposure.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Cobalt is an essential element for humans and is required for the production of vitamin B_{12} (ATSDR, 1992). It is found in most body tissues, with the highest concentrations occurring in the liver, kidney and bones. Vitamin B_{12} is a coenzyme in many biological reactions including the production of red blood cells, and cobalt has been used to treat anemia. The Recommended Dietary Allowance (RDA) for vitamin B_{12} for adults is 2.4 µg/day, (this amount contains 0.1 µg cobalt) (ATSDR, 1992). Oral exposure to high

levels of cobalt has occurred in humans who consumed beer containing cobalt salts; in the 1960s, cobalt salts were added to beer to improve its foaming qualities. This practice has since been discontinued as it led to several deaths among heavy beer drinkers (8 to 30 pints per day) who consumed doses ranging from 3 to 10 mg cobalt/per day. Less serious effects associated with the consumption of beer containing cobalt compounds included nausea, vomiting and diarrhea. Increased production of red blood cells also occurs in humans after oral exposure to cobalt. Decreased uptake of iodine by the thyroid gland has been observed in humans exposed to short-term doses of 1 mg/kg body weight/day or longer-term doses of 0.54 mg/kg body weight/day.

Developmental effects were not observed in babies born to mothers who were taking cobalt-containing medication to regulate anemia while pregnant (Holly, 1955 as cited in ATSDR, 1992). Reproductive effects were not observed in the people who died after exposure to high cobalt levels in beer. Some reproductive effects have been observed in animals (adverse effects on the testes and increased length of the estrous cycle), however, the significance of these effects for humans is not clear as the cobalt doses used in these studies were much higher than those to which humans are usually exposed.

Inhalation Exposure

Inhalation of cobalt can affect the respiratory system and if sufficient quantities are inhaled (0.003 mg/m^3), irritation, wheezing, asthma and pneumonia can result. Occupational exposure to cobalt concentrations of 0.038 mg/m^3 for six hours resulted in breathing difficulties, although these levels are approximately 10,000 to 100,000 times the typical outdoor air concentration. Individuals can also develop sensitivity to cobalt through occupational exposure to concentrations =0.007 mg/m^3, and subsequent exposures can result in skin rashes or asthma attacks.

Dermal Exposure

Weight loss has been reported in animal studies conducted with various cobalt compounds. Necrosis of the thymus was observed in rats exposed to 19 mg/m^3 as cobalt sulfate, and hyperplasia of the mediastinal lymph nodes was found in mice exposed to 11.4 mg/m^3. Neurological effects such as congestion in the vessels of the brain/meninges was reported in rats and mice exposed to =19 mg/m^3 as cobalt sulfate. Several reproductive impacts have been reported including testicular atrophy and decrease in sperm motility in rats and mice exposed to 1.14-19 mg/m^3 for intermediate and acute length exposure times, respectively.

Reference Dose for Chronic Oral Exposure (RfD)

An RfD is not available on the US EPA IRIS website, as cobalt is considered an essential element. The US EPA NCEA has developed a provisional oral RfD of 0.02 mg/kg/day (US EPA Region 3, 2003).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC is not available on the IRIS website, but the provisional inhalation RfD value from US EPA NCEA is 5.7E-6 mg/kg/day (US EPA Region 3, 2003).

Carcinogenic Effects
Cobalt has not been shown to cause cancer in humans. One occupational study reported an increased incidence of lung cancer deaths amongst workers exposed to cobalt in comparison to a control population that had not been exposed to cobalt. The difference between the exposed workers and the control population was not considered to be statistically significant. Additionally, the presence of characteristic lung diseases associated with occupational exposure to cobalt was not documented, although concomitant exposure to arsenic and nickel obscure the observed effects. Tumors have not been observed in humans with prostheses (i.e., artificial knees), which contain cobalt alloys.

Exposure to cobalt oxide dust in hamsters did not lead to an increased incidence of lung tumors in comparison to the control population. Intramuscular injection of cobalt oxide resulted in the production of tumors in rats but not in mice (Gilman 1962 as cited in ATSDR, 1992). Based on animal data, the International Agency for Research on Cancer has classified cobalt as possibly carcinogenic for humans. However, a US EPA classification on carcinogenicity is not available at this time (US EPA, 2004).

Carcinogenic Risk from Oral Exposure
An oral slope factor for cobalt is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for cobalt is not available from the US EPA IRIS website, but a provisional value of 9.8 $(mg/kg/day)^{-1}$ is provided by US EPA NCEA (US EPA Region 3, 2003).

Summary

Oral chronic RfD	0.02 mg/kg/day	US EPA Region 3, 2003
Inhalation RfD	5.7E-6 mg/kg/day	US EPA Region 3, 2003
Oral Slope Factor	not found	US EPA, 2004
Inhalation Slope Factor	9.8 $(mg/kg/day)^{-1}$	US EPA Region 3, 2003

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1992. Toxicological Profile for Cobalt.

United States Environmental Protection Agency (US EPA) Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS). URL: http://www.epa.gov/iris/

COPPER

Pharmacokinetics

Oral Exposure
Absorption of copper occurs primarily through the gastrointestinal tract, and the relative rate of uptake is related to the dose administered. For example, when adults were administered a low copper diet (0.78 mg copper per day), 55.6% of the administered copper was absorbed by the gastrointestinal tract as determined by the use of isotopes (ATSDR, 1990). For adults with an adequate dietary intake of copper (1.68 mg copper per day), 36.3% absorption was observed, and for adults with a high daily copper intake (7.53 mg copper per day), only 12.4 % absorption was found. Copper absorption in adults is saturable; the percent absorption decreases with increases in daily copper intake. Total retention of copper increased with dietary intake and appropriate balance is maintained even at the lowest concentration studied (0.78 mg copper per day). Copper absorption and metabolism is decreased as a result of competition other metals such as iron and zinc for binding sites on metallothionein, whereas molybdenum can totally inhibit copper retention (ATSDR, 1990). The liver is the major organ involved in the distribution of copper throughout the body, with distribution of copper to other tissues occurring via the blood stream. Ceruloplasmin (a protein which can bind 6 to 8 Cu (II) atoms) and serum albumin appear to be the major carriers (ATSDR, 1990). The highest concentrations of copper are found in the brain, kidney, heart, liver and pancreas (ATSDR, 1990). The major elimination pathway for copper in the liver is via bile, which accounts for approximately 80% of the copper exiting the liver. Pregnancy is associated with increased copper retention, and is likely due to decreased biliary excretion resulting from the hormonal changes that typically occur. Urinary excretion and sweating are minor contributors to copper removal (ATSDR, 1990).

Inhalation Exposure
No studies were located regarding the rate and extent of absorption following inhalation exposure of humans to copper. Limited data on animals reveal copper oxide absorption in alveolar capillaries 3 hours after rats were exposed to a welding dust aerosol from pure copper wires. The half-life of copper sulfate in the lungs of rats was estimated to be 7.5 hours following intratracheal instillation of 20 µg copper per rat.

Dermal Exposure
Animal studies demonstrate that copper can pass through dermal barriers when applied with certain vehicles (e.g., salicylic acid or phenylbutazone). However, studies suggest that copper (copper chloride>copper sulphate) is poorly absorbed through intact skin with <6% of copper absorbed following *ex vivo* application to human skin.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Copper is an essential element for humans and is found widely throughout the body. Adverse health effects can be linked to both copper deficiency as well as excessive copper levels. Copper deficiency is demonstrated by anemia, neutropenia and bone abnormalities, but is rarely observed in clinical situations (ATSDR, 1990). Copper is considered essential for the development of structural and enzymatic proteins; enzymes regulating cellular respiration, free radical detoxification, iron metabolism, neurotransmitter function and synthesis of connective tissue contain copper (ATSDR, 1990). Regulation (activation and repression) of gene transcription also requires copper (ATSDR, 1990). Copper concentrations are regulated in the body by a process called homeostasis.

Copper is rarely toxic unless very large amounts are ingested. The available toxicity data associated with oral consumption of copper are limited to ingestion of water with very high copper concentrations or suicide attempts involving copper sulphate. Chronic exposure to drinking water containing (dose approximately 0.06 mg copper/kg/day - 4.2 mg copper/day for a 70-kg adult) resulted in nausea, vomiting and abdominal pain shortly after consumption of the water (ATSDR, 1990). The gastrointestinal difficulties stopped after an alternate water supply was found for the affected persons. Similar symptoms were observed in patients who had attempted suicide (although dose information may be inaccurate as it was provided by the patients). The gastrointestinal effects were produced at doses ranging from 0.07 to 1,421 mg copper/kg (4.9 to 99,470 mg copper for a 70-kg adult) (ATSDR, 1990).

Wilson's Disease is a genetic disorder associated with impaired transport of copper from the liver to the bile, thereby resulting in increased copper concentrations in the liver, as they are not able to maintain homeostasis. Developmental effects have not been observed in children of mothers with Wilson's Disease or healthy humans (ATSDR, 1990). Infants and children under 1 year old are unusually susceptible copper toxicity because they have not developed the homeostatic mechanism to remove copper from the body. (ATSDR, 1990) Another genetic condition, which increases the susceptibility to copper toxicity, is a deficiency in the enzyme glucose-6-phosphate dehydrogenase. Individuals with liver disease are also susceptible to copper toxicity because of the critical role the liver plays in eliminating copper from the body (ATSDR, 1990).

As copper is considered an essential element for humans there are two types of exposure limits that are considered (a) the minimal daily intake so that a person will not be suffer from copper deficiency and (b) the maximal permissible daily intakes so that a person will not suffer from copper toxicity. Developmental toxicity has been found in mice, mink and hamsters that were fed a high copper diet or injected with copper (ATSDR,

1990). Reproductive effects have not been observed in human populations exposed to high copper levels. Copper containing intrauterine devices are used as a method of birth control and animal studies have shown that the copper wires contained within these devices are the contraceptive agent.

Inhalation Exposure
Workers exposed to copper dust reported a number of respiratory symptoms (respiratory irritation, including coughing, sneezing, thoracic pain, and runny nose), gastrointestinal (anorexia, nausea, diarrhea), hematological (decreased hemoglobin and erythrocyte), hepatomegaly, endocrine (hypophyseal adenoma), reproductive (impotence) and other systemic effects (eye irritation, chills, fever, dry mouth, headache). Mild respiratory effects (e.g., alveolar thickening) have been observed in hamsters, mice and rabbits exposed to airborne copper sulfate (ATSDR 1990).

Dermal Exposure
Dermal exposure to copper can result in dermatitis (ATSDR 1990).

Reference Dose for Chronic Oral Exposure (RfD)
Minimal Daily Intake
The World Health Organization (WHO) has determined the minimal daily copper intake for adults to be 0.020 mg copper /kg body weight per day which is equivalent to 1.4 mg copper per day for the average 70 kg adult (US EPA, 2004). For children, the WHO concluded the minimal daily copper intake should be 0.050 mg/kg body weight per day (equivalent to 0.75 mg copper per day for a 15 kg child). The minimal daily copper intake was determined as the amount of copper needed for a child or adult to function properly while accounting for variables such as differences in copper absorption, retention and storage.

Maximal Permissible Daily Intake
The maximal permissible daily intake for adults is a bit uncertain but is believed to be in the range of 2-3 mg copper/day. The maximal permissible concentration is based on studies indicating that people exposed to higher levels of copper in drinking water experienced temporary gastrointestinal distress and incorporates a safety factor of two (i.e., the maximal concentration is half the level at which gastrointestinal effects were observed). There is currently only limited information about the level of copper ingestion from food that would result in an adverse health effect.

An RfD for elemental copper is not available at this time on the IRIS website (US EPA, 2004). However, an oral RfD of 0.04 mg/kg/day is listed on The Health Effects Assessment Summary Table (HEAST) based on a LOAEL from a single oral dose of 5.3 mg in a human study (with the occurrence of gastrointestinal irritation as the critical effect) (US EPA, 1997).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for elemental copper is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified copper and copper compounds as Class D – not classifiable as to human carcinogenicity. This classification is used for substances for which inadequate data are available to make a carcinogenicity assessment. Specifically, for copper and copper compounds there are no human data, animal bioassay data is inadequate and mutagenicity test results are unclear (US EPA, 2004)

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for copper (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation unit risk value is not available for copper (US EPA, 2004).

Summary

Oral Chronic RfD	0.04 mg/kg/day	gastrointestinal irritation	US EPA, 1997
Inhalation RfC		not available at this time	US EPA, 2004
Oral Slope Factor		not available at this time	US EPA, 2004
Inhalation Unit Risk		not available at this time	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR).1990. Toxicological Profile for Copper.

United States Environmental Protection Agency (US EPA). 1997. Health Effects Assessment Summary Tables (HEAST), FY 1997 Update. EPA-540-R-97-036. Prepared for the Office of Solid Waste and Emergency Response.

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Copper. URL: http://www.epa.gov/iris/

N-BUTYLBENZENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
No information was found on the pharmacokinetics of n-butylbenzene in humans or animals.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
No information was found on the toxicity of n-butylbenzene to humans or animals.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD is not available for n-butylbenzene on the US EPA IRIS website, but an RfD_o provisional value from the US EPA NCEA of 4E-2 mg/kg/day was listed on an April 2003 version of the US EPA Region 3 table (this value has since been removed) (US EPA Region 3, 2003).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC was not found for n-butylbenzene.

Carcinogenic Effects
Carcinogenicity information was not found for n-butylbenzene.

Carcinogenic Risk from Oral Exposure
An oral slope factor was not found for n-butylbenzene (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor was not found for n-butylbenzene (US EPA, 2004).

Summary

Oral Chronic RfD	4E-2 mg/kg/day	US EPA Region 3, 2003
Inhalation RfC	not found	US EPA, 2004
Oral Slope Factor	not found	US EPA, 2004
Inhalation Slope Factor	not found	US EPA, 2004

References

United States Environmental Protection Agency (US EPA) Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 4/25/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS). URL: http://www.epa.gov/iris/

P,P'-DICHLORODIPHENYL TRICHLOROETHANE (DDT), P,P'-DICHLORODIPHENYL DICHLOROETHYLENE (DDE), P,P-DICHLORODIPHENYL DICHLOROETHANE (P,P-DDD)

Pharmacokinetics

The p,p' isomer is one form of dichlorodiphenyl trichloroethane (DDT), dichlorodiphenyl dichloroethylene (DDE) and dichlorodiphenyl dichloroethane (DDD), and is found in all technical grade sources of DDT (DDE and DDD are degradation products of DDT) (ATSDR, 2002). For the purposes of this pharmacokinetics discussion, DDT, DDE and DDD will be discussed generally, without reference to specific isometric structure.

Oral Exposure

The major DDT, DDE and DDD exposure pathway for humans is oral (via food), although small amounts may be taken up by inhalation (which is limited by the large particle size) or dermal exposure (ATSDR, 2002). Absorption following oral exposure has been characterized in humans by measuring serum and adipose tissue loads of DDT, DDE and DDD, and from measurement of the primary metabolite bis(p-chlorophenyl) acetic acid (DDA) in the urine. DDT, DDE and DDD are preferentially absorbed by the intestinal lymphatic system (ATSDR, 2002). Human volunteer studies where individuals were orally administered DDT in doses ranging from 5 to 20 mg/kg/day for up to 6 months found the ratio of DDT in adipose tissue versus blood was approximately 280:1 (ATSDR, 2002). Chronic exposure studies administering oral doses of DDT up to 20 mg/day (equivalent to 0.3 mg/kg/day) found DDT in the serum at peak concentrations after 3 hours of digestion (ATSDR, 2002). Evidence of gastrointestinal absorption of DDT, DDE and DDD following oral administration in experimental animals is inferred by the presence of metabolites in the urine and bile, and the induction of tumors and other toxic effects (ATSDR, 2002). DDT, DDE and DDD are lipid-soluble and readily distributed via lymph and blood to all body tissues, with storage capacity equivalent to the lipid content of the tissue. The storage capacity in adipose tissue of DDT products increases in the following order: p,p'-DDD, o,p'-DDT < p,p'-DDT < p,p'-DDE. The biological half-life for DDT products increases as follows DDE > DDT > DDD, based on relative chemical stability in the body, the efficiency of excretory mechanisms and potential transport in and out of fat deposits (ATSDR, 2002). Excretion is slow, with the majority occurring via urine in the form of DDA and other metabolites. A volunteer study found DDT ingested at a rate of 35 mg/day (approximately 0.5 mg/kg) for up to 18 months is rapidly excreted as DDA for the first few days, with a steady-state level of approximately 13 to 16% of the administered dose held for 56 weeks (ATSDR, 2002). A smaller proportion of DDT, DDE and DDD excretion occur via feces (following biliary excretion) or breast milk.

Inhalation Exposure
No studies have been found to quantify the rate or extent of absorption of DDT, DDE or DDD via inhalation in humans or animals (ATSDR, 2002). Occupational studies on humans suggest inhalation and dermal exposure are the most likely sources of exposure, although absorption from the lungs is considered insignificant, and more likely from ingestion via swallowing (ATSDR, 2002).

Dermal Exposure
Absorption of DDT, DDE and DDD following dermal exposure is also considered limited in humans and animals. A monkey study found 3.3 % of DDT (in soil) administered to the abdomen was absorbed after 24 hours (ATSDR, 2002).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
There have been numerous studies on the effects of DDT and its degradation products (DDE and DDD) on animals, with limited studies focusing on humans. Most human studies are from studies of occupationally exposed workers, only a few of which are epidemiological studies (ATSDR, 2002). DDT is most recognized for damaging the nervous system causing a wide variety of effects ranging from mild altered sensations to tremors and convulsions. Humans are able to tolerate up to 285 mg/kg oral doses of DDT without fatalities, although it is noted that in that study vomiting was induced, and the true absorbed amount was unknown. Human studies also suggest high concentrations of DDT and DDE may affect the hormonal endpoints such as the duration of lactation, maintenance of pregnancy and fertility. The liver is a target for DDT, DDE and DDD toxicity in experimental animals. Numerous experimental animal studies have also found DDT, DDE and DDD to cause liver and other cancers, while human exposure has been shown to have a possible link to breast cancer. Interestingly, while animal studies have clearly found evidence of DDT impacts on the liver, human occupational and volunteer studies have found only mild liver alterations with no clinical significance (ATSDR, 2002).

Inhalation Exposure
Occupational exposure to DDT involves multiple routes of exposure with the primary contact most likely being inhalation and dermal. However, ingestion via swallowing rather than inhalation via the lungs is a more likely uptake mechanisms, so epidemiological studies of occupational exposure are discussed under oral exposure (ATSDR 2002).

Dermal Exposure
In rats, guinea pigs, and rabbits exposed to acute dermal doses ranging from 50 to 200 mg DDT/kg, respiratory, cardiovascular, hematological, hepatic, dermal and neurological effects have been reported (ATSDR 2002).
Reference Dose for Chronic Oral Exposure (RfD)
The RfD for p,p'-DDT is 5E-4 mg/kg/day based on the results of a 27-week rat feeding study with liver lesions as the critical endpoint (US EPA, 2004a). NOAEL and LOAEL values of 1 ppm (0.05 mg/kg/day) and 5 ppm (0.25 mg/kg/day), respectively, were derived from the study (US EPA, 2004a). An uncertainty factor was 100 was applied to the NOAEL to derive the RfD. The overall uncertainty factor accounted for interspecies conversion (10) and sensitive subpopulations (10). Confidence in the oral RfD is reported as medium for the quality of the study, database and RfD.

The RfD for p,p'-DDE is not available at this time (US EPA, 2004b).

The RfD for p,p'-DDD is not available at this time (US EPA, 2004c).

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for p,p'-DDT is not available at this time (US EPA, 2004a).

The RfC for p,p'-DDE is not available at this time (US EPA, 2004b).

The RfC for p,p'-DDD is not available at this time (US EPA, 2004c).

Carcinogenic Effects
The p,p'-DDT, p,p'-DDE and p,p'-DDD isomers are all classified as B2 – probable human carcinogen. The status is based on an increased incidence of lung tumor in male and female mice (DDD), liver tumors in male mice (DDD), liver tumors in male and female mice (DDT, DDE) and hamsters (DDE), and thyroid tumors in male (DDD) and female (DDE) rats (US EPA, 2004a; US EPA, 2004b; US EPA 2004c).

Carcinogenic Risk from Oral Exposure
The oral slope factor for p,p'-DDT is 3.4E-1 $(mg/kg/day)^{-1}$ and is based on liver tumors in mice and rats after p,p'-DDT was administered in the diet (US EPA, 2004a). Ten slope factors from 6 studies were within a 13-fold range, with no apparent differences in males versus females.

The oral slope factor for p,p'-DDE is 3.4E-1 $(mg/kg/day)^{-1}$ and is based on liver tumors in mice and hamsters after p,p'-DDE was administered in the diet (US EPA, 2004b).

The oral slope factor for p,p'-DDD is 2.4E-1 $(mg/kg/day)^{-1}$ and is based on liver tumors in male mice after p,p'-DDD was administered in the diet (US EPA, 2004c).

Carcinogenic Risk from Inhalation Exposure

The inhalation unit risk for p,p'-DDT is 9.7E-5 $(\mu g/m^3)^{-1}$ and was calculated from the data used to derive the oral slope factor (US EPA, 2004a).

An inhalation slope factor for p,p'-DDE is not available (US EPA, 2004b).

An inhalation slope factor for p,p'-DDD is not available (US EPA, 2004c).

Summary

p,p'-DDT			
Oral Chronic RfD	5E-4 mg/kg/day	liver lesions	US EPA, 2004a
Inhalation RfC	not available at this time		US EPA, 2004a
Oral Slope Factor	3.4E-1 $(mg/kg/day)^{-1}$	liver tumors	US EPA, 2004a
Inhalation Unit Risk	9.7E-5 $(\mu g/m^3)^{-1}$	liver tumors	US EPA, 2004a
p,p'-DDE			
Oral Chronic RfD	not available at this time		US EPA, 2004b
Inhalation RfC	not available at this time		US EPA, 2004b
Oral Slope Factor	3.4E-1 $(mg/kg/day)^{-1}$	liver tumors	US EPA, 2004b
Inhalation Slope Factor	not available at this time		US EPA, 2004b
p,p'-DDD			
Oral Chronic RfD	not available at this time		US EPA, 2004c
Inhalation RfC	not available at this time		US EPA, 2004c
Oral Slope Factor	2.4E-1 $(mg/kg/day)^{-1}$	liver tumors	US EPA, 2004c
Inhalation Slope Factor	not available at this time		US EPA, 2004c

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2002. Toxicological Profile for DDT, DDE and DDD.

United States Environmental Protection Agency (US EPA). 2004a. Integrated Risk Information System (IRIS) Summary for p,p'-Dichlorodiphenyl trichloroethane (DDT). URL: http://www.epa.gov/iris/

US EPA. 2004b. Integrated Risk Information System (IRIS) Summary for p,p'-Dichlorodiphenyl dichloroethylene (DDE). URL: http://www.epa.gov/iris/

US EPA. 2004c. Integrated Risk Information System (IRIS) Summary for p,p'-Dichlorodiphenyl dichloroethane (DDD). URL: http://www.epa.gov/iris/

DIBENZ(A,H)ANTHRACENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The pharmacokinetics of dibenz(a,h)anthracene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
The toxicity of dibenz(a,h)anthracene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD for dibenz(a,h)anthracene is not available at this time (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for dibenz(a,h)anthracene is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified dibenz(a,h)anthracene as Class B2 – probable human carcinogen (US EPA, 2004). Although no human data were available, there is sufficient indication from animal bioassay data that dibenz(a,h)anthracene may cause cancer in humans. Carcinomas were observed in mice administered dibenz(a,h)anthracene via oral or dermal exposure. Injection of dibenz(a,h)anthracene resulted in tumors at the site of injection in several strains of mice (US EPA, 2004). Dibenz(a,h)anthracene has caused bacterial DNA damage and gene mutations. Cell transformation, resulting from dibenz(a,h)anthracene exposure has also occurred in cultured mammalian cells (US EPA, 2004). Quantitative estimates of slope factors or unit risk values are not available at this time (US EPA, 2004). Carcinogenic assessment of dibenz(a,h)anthracene was conducted using a toxic equivalency factor (TEF) approach. Some PAHs are assigned carcinogenicity relative to benzo(a)pyrene (see PAH toxicity profile for explanation).

Carcinogenic Risk from Oral Exposure
An oral slope factor for dibenz(a,h)anthracene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for dibenz(a,h)anthracene is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD	not available at this time	US EPA, 2004
Inhalation RfC	not available at this time	US EPA, 2004
Oral Slope Factor	not available at this time	US EPA, 2004
Inhalation Slope Factor	not available at this time	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Dibenz(a,h)anthracene. URL: http://www.epa.gov/iris/

DIBROMOCHLOROMETHANE (DBCM) OR CHLORODIBROMOMETHANE

Pharmacokinetics

Oral Exposure

There are few studies available on the pharmacokinetics of dibromochloromethane (DBCM), with most data coming from studies on exposure to a mixture of trihalomethanes (ATSDR, 2003). Oral exposure is the only pathway that has been fully characterized; a study on rats found absorption of DBCM though gavage was rapid, with peak plasma levels occurring less than one hour after exposure (ATSDR, 2003). Gastrointestinal absorption of a mixture of trihalomethanes in corn oil was found to be 60 to 90% complete following rat and mouse exposure at rates of 100 mg/kg and 150 mg/kg, respectively. Distribution following an oral dose of radiolabeled DBCM in animals found that only 1 to 2% of the oral dose (administered as a trihalomethanes mixture) was retained in soft tissues after eight hours. Target tissues were the brain, kidneys, liver, lungs, muscle, pancreas, stomach lining, thymus and urinary bladder in rats and mice. Oral intake studies of rats and mice found the major route of excretion is through the lungs, as either unaltered DBCM or CO_2. Urine excretion is a minor route, accounting for 1 to 5%. DBCM half-life in rats is approximately 1.2 hours, and is 2.5 hours in mice, indicating that excretion is rapid, and tissue accumulation is unlikely.

Inhalation and Dermal Exposure

No studies were found on the absorption, distribution and excretion of DBCM through inhalation or dermal exposure, although based on studies with chemicals having similar molecular structures (i.e., other trihalomethanes), it may be likely that DBCM will also be well absorbed across the lungs and skin in humans and animals (ATSDR, 2003).

Toxicity

Non-Carcinogenic Effects

Oral Exposure

The toxicity of DBCM has been characterized through studies on experimental animals; no studies have been found on the effects of DBCM on humans (ATSDR, 2003). Oral exposure studies have found depression of the central nervous system, and liver and kidney damage are the most common effects (ATSDR, 2003). Central nervous system effects include lethargy, ataxia and sedation at high doses (500 mg/kg/day in rats and mice). Liver damage includes accumulation of fat (causing increased liver weight), hepatocyte vacuoles, alterations in serum cholesterol and triglyceride levels. Liver damage is greater following gavage administration compared to diet or drinking water intake (ATSDR, 2003). Major kidney effects include tubular degeneration and mineralization leading to nephrosis following intermediate or chronic exposure of 50 to 250 mg/kg/day in rats and mice.

Oral uptake of DBCM in experimental animals found NOAELs ranging from 10 mg/kg/day in male mice (administered in water via gavage) to 685 mg/kg/day in mice (administered in water) (ATSDR, 2003). LOAELs ranged from 37 mg/kg/day in male mice (causing liver and kidney damage) to 3700 mg/kg/day in male rats (corresponding to 100% mortality) (ATSDR, 2003). Sex-based differences in acute DCBM toxicity were noted, with males being more sensitive in mice, and females being more sensitive in rats.

Inhalation Exposure
Several studies have reported inhalation exposure of rats to high concentrations (2040 mg/m^3) of DBCM lead to dystrophy and vascular changes in the liver and kidney (ATSDR 2003).

Dermal Exposure
No studies were located regarding health effects in humans or animals following dermal exposure to DBCM.

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for DBCM is 0.02 mg/kg/day based on a NOAEL of 30 mg/kg/day (converted to 21.4 mg/kg/day for continuous exposure) and a LOAEL of 60 mg/kg/day (converted to 42.9 mg/kg/day for continuous exposure) causing hepatic lesions in rats under a subchronic gavage study (US EPA, 2004). The total uncertainty factor is 1000; including a factor of 10 for use of a subchronic study, a factor of 10 for extrapolation from animal data and an additional factor of 10 for the protection of sensitive subpopulations. Confidence in the oral RfD is reported as medium for the quality of the study, database and RfD.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for DBCM is unavailable at this time (US EPA, 2004).

Carcinogenic Effects
Dibromochloromethane is considered a Class C carcinogen – possible human carcinogen. This classification is based on the inadequacy of human studies and limited evidence from mice studies (although DBCM is structurally similar to other trihalomethanes, which are known animal carcinogens) (US EPA, 2004). Carcinogenic effects on mice include increased incidences of hepatocellular adenomas and carcinomas (liver cancer) in females and males following gavage administration (ATSDR, 2003).

Carcinogenic Risk from Oral Exposure
The oral slope factor for DBCM is 0.084 $(mg/kg/day)^{-1}$ and is based on liver tumors found in female mice following gavage administration (US EPA, 2004). An adequate number of individuals were used in the study.

Carcinogenic Risk from Inhalation Exposure
There is no inhalation slope factor available for DBCM (US EPA, 2004).

Summary

Oral Chronic RfD	0.02 mg/kg/day	hepatic lesions	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	0.084 $(mg/kg/day)^{-1}$	liver cancer	US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2003. Draft for Public Comment, Toxicological Profile for Bromoform and Chlorodibromomethane.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Dibromochloromethane. URL: http://www.epa.gov/iris/

1,2-DICHLOROETHANE

Pharmacokinetics

Oral Exposure
1,2-Dichloroethane is well absorbed through the gastrointestinal tract; in animal studies equilibrium blood concentrations were obtained 15 to 60 minutes after oral exposure, probably occurring via passive diffusion (ATSDR, 2001). 1,2-Dichloroethane is widely distributed through the body; animal experiments have shown the highest concentrations in adipose tissue, followed by the bloodstream, liver and lung tissue. Metabolism of 1,2-dichloroethane is rapid, using mixed-function oxidase and glutathione conjugation pathways to produce chloroacetaldehyde, 2-chloroethanol and 2-chloroacetic acid (ATSDR, 2001). Excretion of 1,2-dichloroethane and its metabolites is rapid, and was complete in 48-hours post-exposure in animal studies. A radiolabeling study found 29% of a 1,2-dichloroethane dose was excreted as unchanged parent compound in exhaled air, with lesser amounts excreted via urine (in the form of metabolites) and exhaled air (as CO_2) (ATSDR, 2001).

Inhalation Exposure
1,2-Dichloroethane is also well absorbed through the lungs. In animal studies equilibrium blood concentrations were obtained 2 to 3 hours after inhalation exposure, also likely to occur via passive diffusion (ATSDR, 2001). 1,2-Dichloroethane is widely distributed through the body; animal experiments have shown the highest concentrations in adipose tissue, followed by the bloodstream, liver and lung tissue. Excretion of 1,2-dichloroethane and its metabolites occurs rapidly, and was complete in 48-hours post-exposure in animal studies. An inhalation exposure study in animals has found 84% excretion in the urine (as metabolites) and 7% excretion in exhaled air (as CO_2).

Dermal Exposure
1,2-Dichloroethane is also well absorbed through the skin. In animal studies equilibrium blood concentrations were obtained 1 to 2 hours after aqueous dermal exposure (ATSDR, 2001). As with oral and inhalation exposure routes, distribution following dermal exposure is widespread and excretion is rapid.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
1,2-Dichloroethane can be sufficiently toxic to cause death by cardiac arrhythmia in humans following a single oral dose, and will also cause bronchitis, hemorrhagic gastritis and colitis, hepatocellular damage, renal tubular necrosis and calcification, central nervous system depression and histological changes in brain tissue (ATSDR, 2001). The

effects of oral exposure to 1,2-dichloroethane in animals are well studied and include damage to the immune system, central nervous system, liver and kidneys. Genotoxic effects are also possible following oral exposure.

Inhalation Exposure

Acute inhalation exposure to 1,2-dichloroethane in humans has been shown to cause neurotoxic, nephrotoxic and hepatotoxic effects with respiratory distress, cardiac arrhythmia, nausea and vomiting (ATSDR, 2001). Laboratory animal studies have found short-term exposure targets the immune system, central nervous system, liver and kidneys, and possibly the heart. Genotoxic effects are also possible.

Dermal Exposure

No human studies were found on dermal exposure to 1,2-dichloroethane, although animal studies have found ocular effects (via direct eye contact with vapor), skin lesions and benign pulmonary tumors (via skin exposure to liquid) (ATSDR, 2001).

Reference Dose for Chronic Oral Exposure (RfD)

An RfD is not available for 1,2-dichloroethane on IRIS at this time (US EPA, 2004), however US EPA NCEA has derived a provisional RfD of 2E-2 mg/kg/day (US EPA Region 3, 2003).

Reference Concentration for Chronic Inhalation Exposure (RfC)

An RfC is not available for 1,2-dichloroethane on IRIS at this time (US EPA, 2004), however US EPA NCEA has derived a provisional inhalation RfD of 1.4E-3 mg/kg/day (US EPA Region 3, 2003).

Carcinogenic Effects

1,2-Dichloroethane is classified as Class B2 – probable human carcinogen, based on the induction of several tumor types in rats and mice exposed orally via gavage, and the appearance of lung papillomas in mice following dermal exposure (US EPA, 2004).

Carcinogenic Risk from Oral Exposure

The oral slope factor for 1,2-dichloroethane is 9.1E-2 $(mg/kg/day)^{-1}$ based on the occurrence of hemangiosarcomas (tumors of the blood vessels) in male rats in a gavage study (US EPA, 2004). An adequate test size was used, and effects were significant and dose-related.

Carcinogenic Risk from Inhalation Exposure

The inhalation slope factor for 1,2-dichloroethane is 2.6E-8 $(mg/m^3)^{-1}$ based on the oral slope factor (US EPA, 2004).

Summary

Oral Chronic RfD	2E-2 mg/kg/day		US EPA Region 3, 2003
Inhalation RfD	1.4E-3 mg/kg/day		US EPA Region 3, 2003
Oral Slope Factor	9.1E-2 $(mg/kg/day)^{-1}$	blood vessel tumors	US EPA, 2004
Inhalation Slope Factor	2.6E-8 $(mg/m^3)^{-1}$	blood vessel tumors	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2001. Toxicological Profile for 1,2-Dichloroethane.

United States Environmental Protection Agency (US EPA) Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for 1,2-Dichloroethane. URL: http://www.epa.gov/iris/

DI-N-BUTYLPHTHALATE

Pharmacokinetics

Oral Exposure
No studies were found on the absorption, distribution and excretion of di-n-butylphthalate (DBP) in humans following oral exposure (ATSDR, 2001). Animal studies have shown that DBP is rapidly and extensively absorbed from the gastrointestinal tract and distributed throughout the body, with limited accumulation. Rat, hamster and guinea pig studies have found 63 to 97% of an oral dose is excreted in the urine within 24 hours, and 85 to 100% excreted within 48 hours (ATSDR, 2001).

Inhalation Exposure
No studies were found on the absorption, distribution and excretion of DBP in humans following inhalation exposure (ATSDR, 2001). Animal data suggest absorption in the lungs is rapid and distribution is extensive; a rat study found DBP in all organs examined following exposure, with the greatest concentrations in the brain, lungs, kidneys, liver and testicles after 6 months. No studies were found on the excretion of DBP in animals.

Dermal Exposure
Little is known about the pharmacokinetics of DBP through dermal exposure in humans and animals (ATSDR, 2001). *In vitro* studies suggest slow absorption is possible following dermal application in humans, and in rats approximately 60% of a single dermal dose was excreted in the urine over a 7-day exposure period. Animal data suggest di-n-butyl phthalate is widely distributed following dermal exposure, but absorption is not significant. Excretion of DBP in rats following a single radiolabeled application was 10 to 12% in urine and 1% in feces, with 60% of the applied dose excreted after 7 days (ATSDR, 2001).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Animal studies have found the following effects of DBP following oral exposure: minimal anemia, increased liver weights, changes in kidney weight, decreases in total body weight gain, damage to the male reproductive system and developmental effects (ATSDR, 2001).

Inhalation Exposure
Few studies were found on the toxicity of DBP in humans following inhalation exposure. Reported effects in humans including hypertension, liver and neurological effects, however, occupational exposures often included concomitant exposure to other

plasticizers and effects cannot be attributed solely to DBP (ATSDR, 2001). Animal studies have found inhalation exposure to DBP causes increases in relative lung weights, approximately 13% decrease in body weight gain, and an increase in brain weights in rats (ATSDR, 2001).

Dermal Exposure
The only effect of dermal exposure to DBP in humans that has been reported is slight skin irritation following dermal applications of 520 mg/kg/day (ATSDR, 2001). The only additional effect to animals following dermal exposure is slight kidney damage in rabbits (ATSDR, 2001).

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for DBP is 1E-1 mg/kg/day based on a sub-chronic to chronic oral exposure study in rats with increased mortality as the critical effect (US EPA, 2004). The NOAEL and LOAEL values determined from the study are 125 mg/kg/day and 600 mg/kg/day, respectively. An uncertainty factor of 1000 was applied to account for interspecies variation (10), protection of sensitive subpopulations (10), and for the use of a less-than-chronic study duration and use of only males (10) (US EPA, 2004). As a result of these uncertainties, confidence in the study, database and RfD value is reported as low.

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for DBP is currently unavailable, although health effects data is being reviewed (US EPA, 2004).

Carcinogenic Effects
Di-n-butylphthalate is classified as Class D – not classifiable as to human carcinogenicity (US EPA, 2004).

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for DBP (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for DBP (US EPA, 2004).

Summary

Oral Chronic RfD	1E-1 mg/kg/day	increased mortality	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2001. Toxicological Profile for Di-n-butyl phthalate.

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Dibutyl phthalate. URL: http://www.epa.gov/iris/

ETHYLBENZENE

Pharmacokinetics

Oral Exposure

Absorption of ethylbenzene in liquid state occurs readily through oral, inhalation and dermal exposure pathways. Animal studies indicate ethylbenzene is quickly and effectively absorbed orally. Ethylbenzene metabolites in the urine of rabbits and rats who were administered a single oral dose of 593 and 30 mg/kg, respectively, were between 72-92%. Ethylbenzene is distributed throughout the body and accumulates in adipose tissue, intestine, liver, kidney, and fat (ATSDR, 1999). Ethylbenzene also crosses the placenta and has been detected in umbilical cord blood samples (ATSDR, 1999). Ethylbenzene is primarily metabolized through hydroxylation and conjugation in the liver with no significant differences between oral or inhalation routes. In humans, the major metabolites of ethylbenzene are mandelic acid (64 to 70%) and phenylglyoxylic acid (25%) (US EPA, 1997); however, these compounds are only minor metabolites in laboratory animals. Small doses of ethylbenzene have been shown to be rapidly metabolized and excreted from the body, primarily in the urine. Ethylbenzene is metabolized in the liver and to a lesser extent in the adrenal cortex, mainly through hydroxylation and conjugation reactions (ATSDR, 1999).

Inhalation Exposure

Two human ethylbenzene inhalation studies indicated that 49 to 64% of inhaled doses were retained. Similarly, a rat study found 44% of an inhaled dose (1000 mg/m^3 for 6 hours) was retained. Following inhalation in rat studies, ethylbenzene is distributed throughout the body, with the highest amounts found in the liver and gastrointestinal tract, and lower amounts detected in the adipose tissue. Rat studies also show that ethylbenze is primarily excreted in the urine (83%) followed by expired gases (8%), and feces (0.7%). Excretion in humans ranges from 44 to 100% and the majority of the urinary metabolites are excreted within 6 to 10 hours of exposure initiation.

Dermal Exposure

Dermal exposure to ethylbenzene results in minimal uptake/absorption while liquid ethylbenzene is rapidly absorbed (22 to 33 $mg/cm^2/hr$), based on measurements of urinary metabolites following exposure. The pattern of ethylbenzene elimination following dermal exposure differs significantly from oral and inhalation exposure, as excretion of the metabolite, mandelic acid is approximately 4.6% of the absorbed ethylbenzene dose (ATSDR, 1999).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
No toxicity studies were located regarding effects in humans following oral exposure to ethylbenzene (ATSDR, 1999). Histopathological changes have been observed in the liver and kidney in female rats following administration of 13.6 to 680 mg/kg ethylbenzene by gavage over a 6 month period (ATSDR 1999).

Inhalation Exposure
The major effects observed in humans resulting from exposure to ethylbenzene are pulmonary and ocular irritation (ATSDR, 1999). Acute exposures to elevated atmospheric concentrations of ethylbenzene can cause eye and respiratory tract irritation and central nervous system (CNS) effects (US EPA, 1997). The principal target organs appear to be the lungs, liver, and kidney. Concentrations of 434 mg/m^3 can be highly irritating to the eyes of humans and the threshold for eye irritation has been reported as 879 mg/m^3 (US EPA, 1997). Ethylbenzene vapors have been shown to cause decreased respiration in rats (50%). Laboratory studies also indicate that exposure to ethylbenzene (4340 mg/m^3) during gestation results in adverse developmental effects in rats (skeletal variants) and rabbits (reduced number of offspring).

NOAELs reported from acute inhalation exposure to systemic endpoints ranged from 1,730 mg/m^3 in mice to 10,420 mg/m^3 in rabbits (both species exposed for 4 days, 6 hrs/day; ATSDR, 1999). Acute ethylbenzene exposure to neurological endpoints resulted in NOAELs that ranged from 860 mg/m^3 in rats (exposed once for 4 hours) to 5210 mg/m^3 in rats (exposed for 4 days, 6 hrs/day) (ATSDR, 1999). NOAELs reported from acute exposure to reproductive endpoints ranged from 500 mg/m^3 in female mice (exposed from gestation days 6-15 for 24 hr/day) to 10,420 mg/m^3 in rabbits (exposed for 4 days, 6 hrs/day) (ATSDR 1999). NOAELs reported from chronic exposure to systemic and reproductive endpoints ranged from 1085 to 3260 mg/m^3 in mice (ATSDR 1999).

Dermal Exposure
Direct application of liquid ethylbenzene to the skin and eyes of rabbits caused irritation and injury of conjunctival membranes (ATSDR 1999).

Reference Dose for Chronic Oral Exposure (RfD)
The oral RfD for ethylbenzene is 0.1mg/kg/day based on liver and kidney toxicity observed in a rat study (US EPA, 2004). Groups of female rats were administered doses of 13.6, 136, 408 or 680 mg/kg/day ethylbenzene in olive oil. Histopathological changes were observed in the liver and kidney in the 408 mg/kg/day group. The LOAEL and NOEAL were determined to be 408 and 136 mg/kg/day, respectively. The NOEAL was adjusted for continuous exposure (97.1 mg/kg/day) and an uncertainty factor of 1000 was

applied to derive an RfD of 0.1 mg/kg/day. The uncertainty factor was comprised of a factor of 10 for intraspecies variability, a factor of 10 for interspecies variability and a factor of 10 for extrapolation from a subchronic to chronic effect. Confidence in the study, database and RfD are reported as low.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The US EPA has developed an inhalation RfC is 1 mg/m^3 for ethylbenze based on the results of developmental studies on rats and rabbits. Groups of rats and rabbits were a exposed to concentrations of 0, 434 and 4340 mg/m^3 ethylbenzene for 6 to 7 hours/day, 7-days/week during selected days in the gestation period (1-19 (rats) and 1-24 (rabbits). An additional group of rats was exposed starting 3 weeks prior to mating with the exposure continuing into the gestational period. The study determined that several mild effects were noted in the 4340 mg/m^3 groups including skeletal variation, increased liver and kidney weights and slightly reduced litter size. A lack of developmental effects was noted in the 434 mg/m^3 group and this concentration was, therefore, selected for the NOAEL. An uncertainty factor of 300 was used to derive the RfC of $1mg/m^3$. The uncertainty factor is comprised of (1) a factor of 10 to protect sensitive subpopulations, (2) a factor of 10 to for the lack of multigenerational reproductive and chronic studies and (3) a factor of 3 to adjust for interspecies extrapolation (US EPA, 2004). Confidence in the study, database and RfC are low.

Carcinogenic Effects
Ethylbenzene is classified as Class D by the US EPA – not classifiable as to human carcinogenicity, based on a lack of data in humans and animals (US EPA, 1997).

Carcinogenic Risk from Oral Exposure
An oral slope factor for ethylbenzene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for ethylbenzene is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD	0.1mg/kg/day	liver and kidney effects	US EPA, 2004
Inhalation RfC	1 mg/m^3	developmental effects	US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Toxicological Profile for Ethylbenzene.

United States Environmental Protection Agency (US EPA). 1997. Toxicity Summary for Ethylbenzene. Risk Assessment Information System.
URL: http://risk.lsd.ornl.gov/tox/profiles/ethylbenzene_c_V1.shtml

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Ethylbenzene.
URL: http://www.epa.gov/iris/

FLUORANTHENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The pharmacokinetics of fluoranthene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
The toxicity of fluoranthene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for fluoranthene is 0.04 mg/kg/day based on a study that administered fluoranthene by oral gavage to mice at four different doses (0, 125, 250, and 500 mg/kg/day) for a period of 13 weeks (US EPA, 2004). An additional group of mice were evaluated for baseline blood evaluations. The study investigated a number of clinical endpoints including body weight, food consumption, hematological and serum parameters as wells as organ weight and histopathology. All the mice exposed to fluoranthene demonstrated nephropathy, increased salivation and liver enzymes; however these effects were considered to be insignificant, not adverse at 125 mg/kg/day or not dose-related. Increased food consumption and body weight were observed in mice exposed to 500 mg/kg/day fluoranthene. Liver lesions were observed in mice exposed to 250 (65%) and 500 mg/kg/day (87.5%) fluoranthene, respectively. The LOAEL was 250 mg/kg/day and the NOAEL was 125 mg/kg/day. The uncertainty factor was 3000, and consisted of a factor of 10 to account for interspecies extrapolation, a factor of 10 to account for interspecies variability and a factor of 30 to account for (a) the use of a subchronic study to develop a chronic RfD, (b) the lack of reproductive/development data and (c) lack of adequate toxicity data in a second species. The US EPA indicates that confidence in the RfD is low because, although the study was well designed, the database is lacking in developmental and reproductive toxicity as well as data for a second species. As confidence in the database is low, confidence in the RfD is also low (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for fluoranthene is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified fluoranthene as Class D – not classifiable as to human carcinogenity, due to a lack of human data and inadequate data from animal studies (US EPA, 2004). Several studies have been conducted with mice; however, no increases in tumor incidences were observed and the sample sizes tested were small.

Carcinogenic Risk from Oral Exposure
An oral slope factor for fluoranthene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for fluoranthene is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD	0.04 mg/kg/day	nephropathy	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Fluoranthene. URL: http://www.epa.gov/iris/

INDENO(1,2,3-CD)PYRENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
The pharmacokinetics of indeno(1,2,3-cd)pyrene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
The toxicity of indeno(1,2,3-cd)pyrene and all other PAH congeners is discussed in full in the toxicity profile for PAHs.

Reference Dose for Chronic Oral Exposure (RfD)
An RfD for indeno(1,2,3-cd)pyrene is not available at this time (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for indeno(1,2,3-cd)pyrene is not available at this time (US EPA, 2004).

Carcinogenic Effects
The US EPA has classified indeno(1,2,3-cd)pyrene as Class B2 – probable human carcinogen (US EPA, 2004). Although no human data were available, there is sufficient indication from animal bioassay data that indeno(1,2,3-cd)pyrene will likely cause cancer in humans. Tumors were observed in mice administered indeno(1,2,3-cd)pyrene via lung implants, subcutaneous injection and dermal exposure. Bacterial studies show that indeno(1,2,3-cd)pyrene is mutagenic (US EPA, 2004). Quantitative estimates of slope factors or unit risk values are not available at this time (US EPA, 2003). Carcinogenic assessment of indeno(1,2,3-cd)pyrene was conducted using a toxic equivalency factor (TEF) approach. Some PAHs are assigned carcinogenicity relative to benzo(a)pyrene (see PAH toxicity profile for explanation).

Carcinogenic Risk from Oral Exposure
An oral slope factor for indeno(1,2,3-cd)pyrene is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for indeno(1,2,3-cd)pyrene is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD	not available at this time	US EPA, 2004
Inhalation RfC	not available at this time	US EPA, 2004
Oral Slope Factor	not available at this time	US EPA, 2004
Inhalation Slope Factor	not available at this time	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Indeno(1,2,3-cd)pyrene. URL: http://www.epa.gov/iris/

IRON

Pharmacokinetics

Oral Exposure
The US National Academy of Science (US NAS) estimated that the maximum bioavailability of iron in food is 18%, based on calculations of heme and non-heme iron absorption from various types of food (US NAS, 2002). The primary mechanism for regulating iron levels in the human body is through changes in the amount of the iron absorbed by the gastrointestinal mucosa. Absorption of dietary iron is influenced by: the amount of iron stored in the body; the amount and chemical type of iron in ingested food; and dietary factors.

Inhalation/Dermal Exposure
No studies could be located on the pharmacokinetics of iron resulting from inhalation or dermal exposure.

Toxicity

Non-Carcinogenic Effects
Oral Uptake
Iron is an essential element, and an important component of several proteins including enzymes and hemoglobin. A large portion (approximately 67%) of the iron in the body is found in the hemoglobin of erythrocytes circulating in the blood system. Another 25% of the iron found in the body is stored in a readily mobilizable form. The remaining iron in the body is found in the myoglobin of muscle tissue and in enzymes necessary for oxidative metabolism (US NAS, 2002).

Clinical effects associated with iron deficiency include anemia, developmental delay, cognitive impairment and adverse pregnancy outcomes. Acute iron toxicity effects are well documented, primarily as the result of children who accidentally ingest iron supplements. Symptoms include gastrointestinal distress as well as cardiovascular, metabolic, neurological and hepatic alterations. It is difficult to obtain acute oral toxic doses because they are generally estimated from clinical history in overdose situations. Adverse developmental effects have not been associated with ingestion of supplemental iron intake during pregnancy. There is some controversy over whether individuals with a normal ability to eliminate iron can suffer from a chronic overload due to oral intake; however, the weight-of-evidence indicates that this is possible.

A study (Looker *et al*, 1998 as cited in US EPA, 2001) compared the dietary intake of Americans (6 months to 74 years) to biochemical indices (serum ferritin levels) from the

second National Health and Nutritional Examination Survey (NHANES II) database. The results of the comparison showed that the average iron intake levels (0.15 to 0.27 mg/kg-day) consumed by the population were sufficient to protect against iron deficiency and insufficient to cause toxic effects of iron. The study concluded that the range of 0.15 to 0.27 mg/kg/day represents a NOAEL for chronic daily iron intake.

Chronic iron toxicity has been observed in people with disorders that result in excessive iron absorption, hemoglobin synthesis abnormalities, anemia or frequent blood transfusions. The US NAS (2002) indicates that the weight-of-evidence does not support a causal relationship between elevated iron intake and coronary heart disease as five out of seven studies found no association between serum ferritin and coronary heart disease (Aronow and Ahn, 1996; Frey and Krider, 1994; Magnusson *et al*., 1994; Manttari *et al*.; and Stampfer *et al*., 1993 as cited in US NAS, 2002). However, US NAS (2002) also indicated that elevated iron can not be definitively ruled out as a risk factor in coronary heart disease as high serum ferritin concentration and dietary iron intake have been shown to be risk factors for myocardial infarcation in a study of Eastern Finnish men (Salonen *et al.* as cited in US NAS, 2001). The study also showed that high serum low density lipoprotein (LDL) cholesterol levels in conjunction with elevated serum ferritin levels were a strong risk factor for myocardial infarcation. The study concluded that excessive iron concentrations promote the oxidation of LDL, which elevates the risk of myocardial infarcation (US NAS, 2001). A reanalysis of the same subjects five years later confirmed these conclusions (Salonen *et al.* 1994, as cited in US NAS, 2002).

The American National Academy of Science (US EPA, 2002) has recently developed the following guidelines for iron intake that account for physiological differences during different life stages.

Inhalation and Dermal Exposure
No studies were located regarding toxicity of iron from inhalation or dermal exposures

Provisional Reference Dose for Chronic Oral Exposure (RfD)
The US EPA has not formally assessed iron and therefore has not developed an oral reference dose (RfD). In 1997, it was indicated on HEAST (Health Effects Summary Tables) that there were insufficient data for a quantitative risk assessment. The Superfund Technical Support Center, National Center for Environmental Assessment at the US EPA has derived a provisional references dose for iron to be used at US Superfund sites (US EPA, 2001). The provisional reference dose is currently the only toxicological reference dose available for the assessment of iron at contaminated sites. The toxicological properties of iron have not been assessed by ATSDR or the World Health Organization (WHO).

The US EPA (2001) selected a NOAEL of 0.15 to 0.27 mg/kg/day based on study of dietary iron intake and iron status in the American population. This range of iron intake was sufficient to provide protection against iron deficiency, but insufficient to cause toxic effects. The upper bound of the range was selected and divided by an uncertainty factor of 1 to provide a reference dose (RfD) of 0.3 mg/kg/day. An uncertainty factor of 1 was selected because iron is an essential element.

The US EPA (2001) indicated that the confidence in the RfD is medium, reflecting the high confidence in the critical study and medium confidence in the database. Confidence in the critical study is high based on the large sample size. Overall, confidence in the database is medium as there are insufficient data to determine what chronic dose level is associated with adverse effects in healthy individuals. While a point estimate has been derived in this risk assessment, individual variations in diet, nutritional status, physiology, etc., suggest that a range of values may be more appropriate.

The US EPA (2001) provided the following statement outlining the limitations of the provisional reference dose. The provisional reference dose determined by the US EPA (2001) provides sufficient iron levels to meet the nutritional requirements of adults and adolescents over a lifetime. It does not supply the recommended dietary allowance (RDA) to those members of the population that have greater requirements for a short, less-than-lifetime duration such as infants (7-12 months) and pre-adolescent children (1-8 years), and pregnant women. For shorter-term requirements for these subpopulations, refer to the recommended daily allowances (US NAS, 2002). In addition, the RfD exceeds the allowable intake for infants 0-6 months (US NAS, 2002). Furthermore, this RfD may not be protective of people with inherited disorders of iron metabolism and could be conservative if applied to exposure scenarios involving forms of iron with low bioavailability.

Tolerable Upper Intake Level (UL)

The National Academy of Sciences has also determined a Tolerable Upper Intake Level (UL) for iron of 45 mg/day iron which is based on gastrointestinal distress as an endpoint (US NAS, 2001). A study of Swedish males and females who were taking an iron supplement was used to determine this value (Frykman *et al*. as cited in US NAS, 2001). Several participants complained of gastrointestinal distress and stopped taking the supplement. A LOAEL of 60 mg/kg was determined, however the study was not sufficient to determine a NOAEL. A LOAEL of total iron intake (not just from the supplement) was calculated by adding the LOAEL determined in the Swedish study (60 mg/day) to estimated daily intake of iron from food for Scandinavian men and women (11 mg/day), resulting in a LOAEL of 70 mg/day. An uncertainty factor of 1.5 was selected for extrapolation from a LOAEL to a NOAEL resulting in an upper intake level of 45 mg/day. Conversion of the upper daily intake to an upper daily dose, assuming a body weight of 70 kg, results in an upper daily dose of 0.64 mg/kg/day.

Reference Concentration for Chronic Inhalation Exposure (RfC)
Not available at this time

Carcinogenic Effects
No studies assessing the carcinogenic effects of iron were located.

Carcinogenic Risk from Oral Exposure
Not available at this time

Carcinogenic Risk from Inhalation Exposure
Not available at this time

Summary

Oral Chronic RfD	0.3 mg/kg/day	NOAEL	US EPA NCEA, 2001
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

note: the Oral Chronic RfD is a provisional value.

References

United States Environmental Protection Agency (US EPA), National Center for Environmental Assessment (NCEA). 2001. Risk Assessment Issue Paper - Derivation of the Provisional RfD for Iron and Compounds. SRC SF-021a/11-14-01, dated December 3, 2001.

United States National Academy of Sciences (US NAS), Panel on Macronutrients, Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Use of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board. 2002. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.

LEAD

Pharmacokinetics

Oral Exposure
Gastrointestinal absorption of lead is dependent upon the individual (e.g., age, amount of food in stomach, nutritional status of calcium and iron), as well as the characteristics of the lead ingested (particle size, solubility, and chemical species). Absorption appears to be higher in children (40-50 %) than in adults (15%), with the nutritional status of children also affecting absorption (iron and calcium deficiencies seem to increase lead absorption). Adults exposed to water-soluble lead compounds showed much greater absorption if the lead was not administered with a meal (20 to 70%) compared to those where lead was administered with a meal (3 to 15 %). It appears the mineral content (calcium or phosphate) in the meal will effectively reduce absorption of ingested lead. Absorption of lead in soil is less than that of dissolved lead, and is also depressed by simultaneous ingestion with meals; adults who consumed lead in soil without a meal absorbed 26% of the dose, while those who ingested the lead in soil with a meal absorbed only 2.5% of the lead dose (ATSDR 1999). Absorption of lead may increase during pregnancy and in combination with increased lead mobilization from the bone may contribute to increased blood lead levels during the second-half of pregnancy. The mechanism for lead absorption appears to be saturable, as absorption decreases with increased lead intake.

Lead distribution and elimination is the same regardless of the route of exposure, which indicates the involvement of a common lead transport mechanism. Initial distribution of lead to the tissues is dependent upon on the rate of delivery to the target organs by the blood. Subsequent redistribution can occur between the tissues. Lead in blood is found in the cellular component of the red blood cells. Several pharmacokinetic models have been developed to estimate the distribution of lead between the tissue groups and characterize lead exchange rates between the tissues. Distribution of lead is essentially the same in children and adults, although a larger portion of the body burden resides in the bone in adults. The majority of the body burden is found in the bone (94% for adults and 73 % for children) (ATSDR 1999). As a result, blood lead levels may remain elevated for some time after the exposure has ended. Lead is not distributed uniformly throughout the bone and tends to accumulate at sites, which were undergoing bone development (calcification) at the time of exposure. Bone calcification in children occurs most frequently at the trabecular bone and in adults at both the trabecular and cortical bones. Most of the lead acquired in childhood is not permanently fixed in the bone because the lead is frequently released or excreted during bone resorption. Lead is not metabolized or transformed in the body, although it does form complexes with various proteins. Dietary lead, which is not absorbed by the gastrointestinal tract, is eliminated in the feces.

Inhalation Exposure
Deposition of airborne lead particulate in adults is estimated to be approximately 30 to 50% and is dependent upon particle size and ventilation rate. Of the lead deposited in the lungs, all chemical species of lead are absorbed (about 100%).

Dermal Exposure
Dermal absorption of lead appears to be much less significant that absorption via inhalation or ingestion (0.06% to <0.3 %).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
The toxic effects of lead are not dependent upon route of exposure. Death can result from extremely elevated lead exposures, which correspond to blood lead levels in children of 125 to 750 µg/dL (mean 327 µg/dL). Cardiovascular effects such as cardiac lesions, can result from high lead exposures. The current evidence does not indicate that increased blood lead causes elevated blood pressure. Occupationally exposed individuals with lead poisoning typically exhibit a combination of gastrointestinal symptoms such as abdominal pain, constipation, nausea, and vomiting. Lead affects heme synthesis causing decreased hemoglobin concentrations in blood, which can result in anemia. High lead exposures can result in a bluish tinge to the gums and muscle weakness and joint pain.

Blood lead levels ranging from 60 to >100 µg/dL in occupationally exposed workers has been associated with effects on the kidney. Reversible effects include dysfunction of the proximal tubules as well as increased sodium and uric acid excretion. Chronic lead exposure results in more severe, irreversible kidney effects. Adverse effects on vitamin D metabolism appear to occur in chronically (blood lead levels of 33 to 120 µg/dL) lead exposed children with concomitant deficiencies in calcium, phosphorus and vitamin D. Children appear to be more susceptible to the neurological effects caused by lead as effects occur at lower blood lead levels. Adults demonstrate neurological impairment at blood levels as low as 40 to 60 µg/dL. Several studies have indicated that neurobehavioral impairment does not occur in children with blood levels of approximately 10 µg/dL (Cooney et al, 1989). Several studies indicated that the doubling of blood lead levels from 10 to 20 µg/dL resulted in an average loss of 1 to 3 IQ points on standard IQ exams (ATSDR, 1999). High occupational lead exposures can cause reproductive effects such as spontaneous abortions, miscarriage, and stillbirths. No effect on the rate of spontaneous abortion was observed at blood lead levels of 10 µg/dL. Low levels of lead exposure have not been correlated with congenital abnormalities.

Young children (less than 5 years old) are at highly susceptible to the health effects caused by lead because they have an increased capacity to absorb lead through the gastrointestinal tract in comparison to adults. The behavior of young children such as

sucking thumbs and eating soil results in a greater exposure of young children to lead in soil and dust. Nutritional deficiencies, particularly zinc, may increase some of the toxic effects of lead. Women may also have an increased exposure to lead as pregnancy, lactation and osteoporosis cause bones to lose minerals (breakdown) and thereby releasing lead from the bones into the blood stream and causing increased body burdens of lead. Increased lead in the mother can be transferred to the fetus via the placenta.

Inhalation Exposure
Adult males exposed to particulate lead (0.003 or 0.01 mg lead/m^3) for 23 hours a day for over a period of 3 to 4 months showed decreased levels of enzymes involved in heme biosynthesis (ATSDR 1999).

Dermal Exposure
No studies were located regarding effects in humans or animals after dermal exposure to inorganic lead.

Reference Dose for Chronic Oral Exposure (RfD)
Reference Concentration for Chronic Inhalation Exposure (RfC)
The US EPA (2004) has determined that the effects of lead exposure, particularly changes in blood enzymes and neurodevelopment of children, may occur at blood lead levels so low as to be essentially without a threshold. As a result, the US EPA considers it inappropriate to derive an oral or inhalation toxicity reference values (i.e., RfD or RfC) for lead. Lead will be assessed qualitatively in this report.

Carcinogenic Effects
The US EPA has classified lead as Class B2 - probable human carcinogen based on the available animal data. The available animal data indicate that ingested lead is a carcinogen, with the kidney tumors being the most prevalent type of tumor. Human epidemiological studies indicate lead may cause an increased incidence of overall lung and bladder cancer (ATSDR, 2000), however these studies also lack quantitative information about lead exposure and did not examine confounding factors and concomitant exposure to other metals.

The US EPA (2004) currently does not recommend estimation of carcinogenic risk from lead exposure using standard risk assessment procedures due to the unique pharmacokinetics of lead.

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for lead or lead compounds (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for lead or lead compounds (US EPA, 2004).

Summary

Oral Chronic RfD	not available at this time	US EPA, 2004
Inhalation RfC	not available at this time	US EPA, 2004
Oral Slope Factor	not available at this time	US EPA, 2004
Inhalation Slope Factor	not available at this time	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Toxicological Profile for Lead.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Lead. URL: http://www.epa.gov/iris/

MANGANESE

Pharmacokinetics

Oral Exposure
Manganese is typically found in human tissue, blood, serum and urine. Adult humans generally maintain consistent manganese levels in tissues, irrespective of manganese intake. Manganese absorption and excretion are regulated; absorption occurs primarily through oral and inhalation exposure routes. The rate of uptake across the gastrointestinal tract is variable, but typically ranges from 3 to 5% in humans (ATSDR, 2000). There does not appear to a difference in uptake across the gastrointestinal tract if the manganese is consumed in food or water (ATSDR, 2000). Absorption of manganese may be age dependent as studies have shown greater uptake in young children than in adults. Dietary iron levels also influence, manganese uptake, as low iron levels lead to increased manganese uptake. Manganese metabolism is not well understood in human systems, but appears to involve oxidation of manganese from Mn(II) to Mn(III). Excretion of manganese occurs primarily via bile, although other minor routes of elimination include urine, breast milk and sweat. Manganese is removed from the blood by the liver, where it conjugates with bile and is excreted into the intestine and removed with feces.

Inhalation Exposure
Manganese may be absorbed from both the lungs and the gastrointestinal tract following inhalation of manganese dust, however the relative rates of absorption are not known (ATSDR, 2000).

Dermal Exposure
Manganese uptake across intact skin is expected to be extremely limited (ATSDR, 2000).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Manganese is an essential element for humans and is found widely throughout the body. Adverse health effects can be linked to both manganese deficiency as well as excessive manganese levels. Bone mineralization, protein and energy metabolism, metabolic regulation, cellular protection from free radicals are all functions that require manganese. Manganese is also a component of metalloenzymes and can act as an enzyme activator (ATSDR, 2000).

Inhalation Exposure
Chronic exposure to high levels of manganese has caused permanent neurological damage in occupationally exposed miners (ATSDR, 2000). Chronic exposures to lower

manganese concentrations have resulted in loss of coordination and balance, as well as a decreased ability to perform rapid hand movements (ATSDR, 2000). Inhalation of particulate matter containing manganese may also lead to an inflammatory response in the lungs (ATSDR, 2000).

Dermal Exposure
Organic forms of manganese (maneb and mancozeb) have been found to cause allergic contact dermatitis reactions.

Reference Dose for Chronic Oral Exposure (RfD)
The US EPA has developed an RfD of 0.14 mg/kg/day based on a compilation of assessments of typical dietary intake of manganese. In 1989, the US Food and Nutrition Board of the National Research Council (NRC) determined an estimated safe and daily dietary intake of manganese to be 2 to 5 mg/day and indicated that 10 mg/day may be safe for occasional intake. Subsequently, some nutritionists have indicated that the NRC level of 2 to 5 mg/day may be too low, based on recent changes in diet that include a greater consumption of meats and processed food and less whole grains and recommend levels of 3.5 to 7 mg/day to prevent sub-optimal manganese levels in the population (US EPA, 2004). The World Health Organization has also examined manganese levels in adult diets and that the daily average ranges from 2.0 to 8.8 mg/day. The World Health Organization conducted manganese balance studies and found that 2 to 3 mg/day is adequate and that 8 to 9 mg/day is "safe" for adult populations (US EPA, 2004). High manganese concentrations in diet are generally associated with high consumption of whole-grain cereals, nuts, green leafy vegetables, and tea. It is important to note that manganese bioavailability from vegetarian diets is lower than non-vegetarian diets due to formation of insoluble complexes in the gut (US EPA, 2004). Other studies indicate that typical diets in the US, England and Holland contain manganese concentrations of 2.3 to 8.8 mg/day. Based on a compilation of human studies, the US EPA recommends the use of 10 mg/day as a chronic NOAEL. The Rfd is 0.14 mg/kg/day, based on correction for a 70-kg adult. An uncertainty factor of 1 was applied to the chronic NOAEL because the NOAEL was derived from a cross section of many large human populations and manganese is an essential element.

An epidemiological study of manganese in drinking water and diet of three areas in northwest Greece demonstrates neurological effects in manganese exposed populations, however the exact amount of manganese in the water and diet could not be quantified, thereby precluding the development of a quantitative dose-response relationship. Estimated concentrations of manganese in the diet and water range from 5-15 mg/day (US EPA, 2004). As a result of the possibility that neurological effects could occur at manganese concentrations close to the chronic NOAEL, the US EPA also recommends subtracting background manganese dietary intake (5 mg/day; US EPA Region 9 2002) from the RfD and the use of a modifying factor of three when conducting risk

assessments with non-dietary sources of manganese (i.e., manganese in soil or drinking water). The subtraction of background dietary manganese and the use of a modifying factor of three results in an RfD of 0.024 mg/kg/day.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The US EPA developed an RfC for manganese of 5E-5 mg/m^3, based on decreased neurobehavioral function found in Belgian males occupationally exposed to manganese dioxide dust in a battery factory. The decreased neurobehavioral function entailed significantly slower visual reaction time and erratic control of hand-forearm movement in the occupationally exposed population in comparison with control subjects. The battery factory workers were exposed to an integrated respirable dust (IRD) concentration, which is calculated by multiplying 8-hour TWA occupational exposures for various job classifications by the number of years that individuals had worked at the factory. A LOAEL of 0.15 mg/m^3 was determined by dividing the geometric metric mean of the IRD by the average duration of the workers' exposure. The LOAEL (HEC) was adjusted for continuous exposure (i.e., rather than 5 work days/ week) and is 0.05 mg/m^3. Several other occupational studies were evaluated and lower LOAEL values were calculated, however, manganese exposure in the other occupational studies was the result of an unknown mixture of manganese compounds and concentrations were variable over time. Therefore, the US EPA decided to use a LOAEL of 0.05 mg/m^3 to derive an RfC for manganese.

An uncertainty factor of 1000 was applied to the LOAEL to derive an RfC of 5E-5 mg/m^3. The uncertainty factor consists of: a factor of 10 to account for sensitive subpopulations; a factor of 10 to account for the use of a LOAEL to set the RfC; and a factor of 10 to account for database limitations reflecting less than chronic exposure, lack of developmental data and unquantified differences in the toxicity of different forms of manganese (US EPA, 2004). Confidence in the RfC is medium, reflecting medium confidence in both the primary study and the database.

Carcinogenic Effects
The US EPA has classified manganese as a Class D carcinogen – not classifiable as to human carcinogenicity, due to a lack of human data and inadequate data from animal studies. Several rodent studies have been conducted, however, none of the animals developed significantly increased number of tumors after administration of manganese in comparison to controls or in one case, evidence for a dose-relationship was marginal. Quantitative estimates of slope factors or unit risk values are not available at this time.

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for manganese at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for manganese at this time (US EPA, 2004).

Summary

Oral Chronic RfD	0.14 mg/kg/day*	CNS effects	US EPA, 2004
Inhalation RfC	5E-5 mg/m^3	neurobehavioral impairment	US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

* US EPA recommends subtracting background dietary manganese intake and the use of a modifying factor of three when non-dietary sources of manganese are assessed, resulting in a modified RfD of 0.024 mg/kg/day.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2000. Toxicological Profile for Manganese.

United States Environmental Protection Agency (US EPA) Region 9. 2002. Region 9 PRGs Table 2002 Update.

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Manganese. URL:http://www.epa.gov/iris/

MERCURY

Pharmacokinetics

Oral Exposure

The major sources of mercury exposure for the general population are consumption of fish, which contain methylmercury, and the release of elemental mercury from dental fillings (ATSDR, 1999). Human and animal data are generally limited to inhalation exposure to metallic mercury vapors and oral exposure to inorganic and organic mercury compounds. Metallic mercury is highly lipophilic and diffuses rapidly into the blood to major target organs such as the blood, hair, teeth, kidneys, brain, lungs, liver, and spleen, (ATSDR, 1999). Ingesting small amounts of metallic mercury like the volume found in a standard thermometer (approximately 0.1 mL or 1 g) does not produce symptoms of intoxication (ATSDR, 1999). Reports of ingestion of substantial amounts of elemental mercury indicate that absorption is negligible (<0.01%) (ATSDR, 1999). A number of animal studies indicate oral absorption of inorganic mercury in the 10 to 30% range with the rate in rats and mice being dependent on several factors (e.g., intestinal pH, compound dissociation, age and diet). In animal studies, inorganic mercury tended to distribute to the liver and kidneys. Smaller amounts were also found in the brain and retention was longest in this tissue. Although inorganic mercury compounds do not move easily from the blood of a pregnant woman to the fetus, there is efficient transfer of inorganic mercury from blood to breast milk. Following exposure to metallic mercury, elimination can occur via the urine, feces, and expired air.

Organic mercury compounds are more readily absorbed via oral exposure than inorganic mercury compounds, with methylmercury being the most easily absorbed through the gastrointestinal tract (ATSDR, 1999). Absorption and bioavailability of methylmercury in food, specifically fish and bread, may be affected by other dietary components. Methylmercury distributes readily to all tissues, including the brain and fetus, with highest levels found in the kidneys. Methylmercury may also be secreted in mother's milk. Demethylation occurs in the brain, as well as in other organs, including the kidneys and liver, and may contribute substantially to high concentrations of inorganic mercury in the brain. Organic mercury compounds are excreted primarily via the feces in humans.

Inhalation Exposure

Retention of mercury after exposure to elemental mercury vapor released from liquid mercury is approximately 70 to 80% in human tissues. No studies were located regarding absorption of organic mercurial compounds (e.g., phenyl- or methylmercury) in humans or animals via inhalation exposure.

Dermal Exposure

Dermal absorption of metallic mercury vapor poses a very minor occupational hazard compared to inhalation exposure (ATSDR, 1999). The dermal route is estimated to absorb approximately 2.6% of the amount absorbed by the lung. There was no information found on the dermal absorption of liquid metallic mercury, but unless the skin surface is damaged, it is expected to be minimal. The dermal absorption of dialkyl mercury species is nearly complete (i.e., 100%).

Toxicity

Non-Carcinogenic Effects

Oral Exposure

Organic and Inorganic Mercury

The major target organs of toxicity following oral exposure to inorganic and organic mercury are the kidneys and the central nervous system, respectively. The major effects of organic mercury on the central nervous system include motor disturbances and sensory dysfunction. Reported widespread outbreak of neurological disorders associated with the ingestion of methylmercury-contamination occurred in the Minamata area of Japan and Iraq (ATSDR, 1999). Neurological syndromes observed in these highly exposed populations include tingling sensation in the extremities, impaired peripheral vision, hearing, taste, and smell; slurred speech; muscle weakness; irritability; memory loss; depression; and sleeping difficulties. Prenatal methylmercury exposure in rodents has shown retarded development and impairment of motor function.

Inhalation Exposure

Metallic Mercury

The most commonly reported symptoms after exposure to high concentration metallic mercury vapors include cough, dyspnea, and tightness or burning pains in the chest (ATSDR, 1999). In more severe cases, respiratory distress, pulmonary edema, and pneumonia, have been observed. Other major target organs for the inhalation of metallic mercury-induced toxicity are the kidneys, the central nervous and gastrointestinal systems. Rabbits exposed for various durations to mercury vapor have demonstrated neurological effects such as tremors, irritability, nervousness, insomnia, memory loss, neuromuscular changes, headaches, polyneuropathy and performance deficits in tests of cognitive function.

Organic and Inorganic Mercury

Exposure to organic mercury via inhalation is extremely rare. However, dyspnea, respiratory depression, and respirations frequently obstructed by mucus were observed in a farmer who had treated grain with unknown amounts of phenylmercuric acetate (ATSDR, 1999). Gastrointestinal effects, similar to metallic mercury exposure, have been reported in several case studies of humans exposed to organic mercury compounds.

Dermal Exposure
Acute and chronic occupational inorganic mercury exposure has been described to result in contact dermatitis. Application of ammoniated mercury ointment to skin in children resulted in itching, flushing, swelling, and conjunctivitis. A woman exposed to a topical applications of a cream containing 17.5% mercuric ammonium chloride for 18 years demonstrated mild tremors, anxiety, and depression. Dermal exposure to methylmercury or phenylmercury in humans may cause rashes and blisters on the skin (ATSDR, 1999).

Reference Dose for Chronic Oral Exposure (RfD)
An RfD for chronic oral exposure is not available from the US EPA for elemental mercury (US EPA, 2004).

The US EPA (2004) has developed an RfD for mercuric chloride of 3E-4 mg/kg/day, based on the results of several rat studies (feeding and subcutaneous studies) that were used to recommend a Drinking Water Equivalent Level (0.010 mg/L). The Drinking Water Equivalent Level was then used to back calculate a reference dose concentration using a standard drinking water ingestion rate of 2L per day and adult body weight of 70 kg. An uncertainty factor of 1000 was applied to the LOAEL derived from the rat studies, including (1) a factor of 10 for the use Brown Norway rats in the study, (2) a factor of 10 for the use of a LOAEL rather than a NOAEL for RfD derivation and (3) a factor of 10 to account for the use of subchronic studies, intraspecies extrapolation and sensitive human populations. Confidence in the database and the RfD are high.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for elemental mercury is 3E-4 mg/m^3 and is based on several human occupational inhalation studies focusing on hand tremors, increased memory disturbances, and evidence of autonomic dysfunction as critical effect endpoints. A LOAEL of 0.025 mg/m^3 was determined based on average exposure concentrations from of approximately 0.025-0.03 mg/m^3, over a period of about 15 years. The LOAEL is based on an 8-hour air concentration (TWA) occupational exposure and extrapolation from blood levels. The RfC contains an uncertainty factor is 30, including a factor of 10 for the protection of sensitive human subpopulations and the use of a LOAEL rather than a NOAEL and a factor of 3 was for lack of developmental and reproductive studies in the database.

An RfC for mercuric chloride is unavailable at this time.

Carcinogenic Effects
Elemental mercury is classified as a Class D carcinogen - not classifiable due to inadequate human and animal data, based on inadequate human and animal data. Epidemiological studies are limited by the presence of confounding factors and concomitant exposures to multiple chemicals and have not demonstrated a correlation between exposure to elemental mercury vapor and carcinogenicity.

Mercuric chloride is classified as a Class C carcinogen – a possible human carcinogen, based on a lack of human data and limited evidence in rodents (US EPA, 2004).

Carcinogenic Risk from Oral Exposure

Oral slope factors are unavailable for elemental mercury and mercuric chloride, as limited or inadequate human and animal carcinogenicity data are available (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure

Inhalation slope factors are unavailable for elemental mercury and mercuric chloride, as limited or inadequate human and animal carcinogenicity data are available (US EPA, 2004).

Summary

Oral Chronic RfD ($HgCl_2$)	3E-4 mg/kg/day	autoimmune effects	US EPA, 2004
Inhalation RfC (Hg)	3E-4 mg/m^3	neurological effects	US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Toxicological Profile for Mercury.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Mercury. URL:http://www.epa.gov/iris/

METHYL TERT-BUTYL ETHER (MTBE)

Pharmacokinetics

Oral Exposure
No studies were found on the absorption of methyl tert-butyl ether (MTBE) in humans following oral exposure, although rapid absorption across the gastrointestinal tract is expected based on the findings of animal studies (ATSDR, 1996). Rats receiving a single oral dose of 0.379 mg/kg MTBE showed peak blood concentrations of 5.9 μg/mL in 0.9 hours. Rats receiving single oral doses of 40 or 400 mg/kg MTBE in water had MTBE and tert-butanol detected in plasma within 15 minutes (the oral bioavailability of MTBE was calculated to be 58% in males and 81% in females). No studies have been found on the distribution of MTBE following oral exposure in humans, although distribution studies in rats have found MTBE in the fatty tissue (adipose cells), brain, liver and kidneys) (ATSDR, 1996).

Inhalation Exposure
Findings from a volunteer study of motorists found MTBE, a gasoline additive, is rapidly absorbed across the lungs following inhalation exposure and is metabolized to tert-butanol. No studies have been found on the distribution of MTBE following inhalation exposure, but once in the bloodstream, MTBE is rapidly excreted via the lungs, and more slowly via urine. One study found exhalation excretion was nearly complete after 6 hours, while kidney excretion was complete after 36 hours (ATSDR, 1996). Radiolabeling studies have found limited excretion of MTBE via feces. Pharmakokinetic data for animals is limited to studies on rats, which have found absorption of MTBE through inhalation exposure is also rapid, with low accumulation in tissues (ATSDR, 1996). Distribution of MTBE is widespread in rats, targeting the fatty tissue (adipose cells), brain, liver and kidneys) (ATSDR, 1996).

Dermal Exposure
No studies were found on the absorption and distribution of MTBE in humans following dermal exposure, although it is assumed to be at a much lower rate than through inhalation or oral exposure (ATSDR, 1996). Rat studies have found absorption is greater with higher doses, distribution occurs in the fatty tissue, brain, liver and kidneys, and excretion via urine and exhaled air is rapid.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
The main effects of MTBE via oral exposure are on the central nervous system, these include central nervous system (CNS) depression, ataxia, tremors, labored breathing and

loss of righting reflex in rats at doses greater than 4080 mg/kg. These effects showed rapid onset in the study, but were gone or markedly reduced within 24 hours (ATSDR, 1996). Oral exposure of MTBE by rats has also been shown to cause labored respiration, diarrhea and histological lesions, hematological effects and relative increases in liver and kidney weights (ATSDR, 1996).

Inhalation Exposure
Inhalation exposure to methyl tert-butyl ether (MTBE) is the most common and harmful pathway. A volunteer study of cab drivers, health workers and students fueling their vehicles with MTBE-enhanced fuel reported various respiratory effects including headaches, nausea, vomiting, burning sensations in the nose, mouth or throat, cough, dizziness, and eye irritation (ATSDR, 1996). Increased kidney and liver weights were reported in rat and mice studies at rates between 10,815 and 28,843 mg/m^3 (ATSDR, 1996).

Inhalation uptake studies of the toxicity of MTBE found NOAELs ranging from 5.0 mg/m^3 following a 1-hour exposure in humans (focusing on systemic effects) to 28,843 mg/m^3 in studies on rats, mice and rabbits over various durations (acute to chronic) (focusing on numerous systems) (ATSDR, 1996). Inhalation uptake LOAELs for MTBE ranged from 2,884 mg/m^3 from a 13 week, 5 days/week, 6 hours/day exposure duration in rats (causing increased motor activity in females, and various hematological effects and increased liver and kidney weights in males) to 754,590 mg/m^3 from a 3 to 12 minute exposure duration in male mice (ATSDR, 1996).

Dermal Exposure
Dermal exposure to MTBE has not been well characterized. Toxic dermal effects included blanching and epidermal thickening upon application of 10,000 mg/kg MTBE to the intact or abraded skin of rabbits, with slight diarrhea developing in rats following a dose of 40 mg/kg (ATSDR, 1996).

Reference Dose for Chronic Oral Exposure (RfD)
An RfD for MTBE is not available at this time (US EPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for MTBE is 3 mg/m^3 based on a 2-year chronic inhalation exposure study in rats with critical effects including increased liver and kidney weights and increased kidney lesions (in females) (US EPA, 2004). The NOAEL and LOAEL values were determined to be 1453 mg/m^3 (adjusted to a human equivalent concentration of 259 mg/m^3) and 10,899 mg/m^3 (adjusted to a human equivalent concentration of 1946 mg/m^3), respectively (US EPA, 2004). The uncertainty factor for this RfC is 100 (based on protection of sensitive subpopulations (10), interspecies extrapolation (3), and database deficiencies in information on urinalysis results, serum chemistry, and limited

reporting of clinical signs during exposure (3)). The confidence in the study, database and RfC value are medium.

Carcinogenic Effects
No information could be found on the US EPA's carcinogenicity classification for MTBE.

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for MTBE on IRIS at this time (US EPA, 2004). US EPA Region 3 shows an oral slope factor of 4E-3 $(mg/kg/day)^{-1}$ for MTBE derived from an other source and will conservatively be used to assess MTBE carcinogenicity.

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for MTBE at this time (US EPA, 2004).

Summary

Oral chronic RfD	not available at this time		US EPA, 2004
Inhalation RfC	3 mg/m^3	systemic effects	US EPA, 2004
Oral Slope Factor	4E-3 $(mg/kg/day)^{-1}$		US EPA Region 3, 2003
Inhalation Unit Risk	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1996. Toxicological Profile for Methyl tert-butyl ether.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Methyl tert-butyl ether. URL: http://www.epa.gov/iris/

US EPA Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

NAPHTHALENES (NAPHTHALENE AND 2-METHYLNAPHTHALENE)

Pharmacokinetics

Oral Exposure

Limited data are available on the pharmacokinetics of naphthalene in human systems, and no data are available for 2-methylnaphthalene (ATSDR, 2003). Naphthalene is known to be absorbed by the gastrointestinal tract, respiratory tract and skin based on evidence of adverse effects on animals upon exposure (US EPA, 2002). Absorption of naphthalene consumed orally is thought to occur via passive diffusion through the lipophilic matrix of the intestinal membrane; rates of absorption are unavailable. Small doses of 2-methylnaphthalene appear to be rapidly absorbed from the gastrointestinal tract of guinea pigs; at least 80% of a 10 mg/kg dose was absorbed within 24-hours (ATSDR, 2003). Naphthalene has been measured in human body fat and milk, however distribution mechanisms of naphthalene in humans are not known. Naphthalene is able to cross the placenta in high enough concentrations to cause hemolytic anemia in newborn infants whose mothers consume naphthalene during their pregnancy. Targets of 2-methylnaphthalene upon oral exposure include the gall bladder, kidneys, liver, lungs and blood (ATSDR, 2003). Naphthalene metabolism is catalyzed by cytochrome P-450 oyxgenases which produces a reactive intermediary, 1,2-napthalene oxide. Animal studies indicate that naphthalene excretion occurs primarily through the urine, with feces representing a relatively minor excretion pathway. Possible elimination of unmetabolized naphthalene by exhalation following inhalation exposures has not yet been assessed (ATSDR, 2003).

Inhalation Exposure

As mentioned, limited data are available on the pharmacokinetics of naphthalene, although it is known to cause adverse health effects in humans based on prolonged exposure to vapors, which infers absorption via the lungs is possible. Rates of absorption have not been determined, but it is thought that naphthalene may move across the alveolar membrane by passive diffusion. No data have been found on the pharmacokinetics of 2-methylnaphthalene in humans following inhalation exposure (ATSDR, 2003). One guinea pig study found 80% of a 10 mg/kg dose of 2-methylnaphthalene was excreted in the urine within 24 hours, with approximately 10% excreted in the feces; most was in the form of 2-naphthoic acid or its conjugates, and approximately 18% was in the form of 7-methyl-1-naphthol conjugates (ATSDR, 2003).

Dermal Exposure

Absorption of naphthalene through the skin is inferred based on several cases of hemolytic anemia in very young children resulting from the use of diapers stored in mothball containing closets. The addition of sand or clay soil to radiolabeled naphthalene

applied to shaved rat skin decreased the rate of absorption somewhat (absorption half-life was 2.1 hours for naphthalene; 2.8 hours for naphthalene with clay and 4.6 hours for naphthalene with sand) (ATSDR, 2003). The rate of absorption did not affect the total amount of naphthalene absorbed over a 48-hour period. The decreased naphthalene absorption associated with the presence of clay is likely due to the higher organic content in clay (4.4%) compared to sand (1.6%) (ATSDR, 2003). No data have been found on the pharmacokinetics of 2-methylnaphthalene in humans or animals following dermal exposure (ATSDR, 2003).

Toxicity

Non-Carcinogenic Effects

Oral Exposure

There are three main types of health effects associated with naphthalene exposure: hemolysis (causing decreased oxygen carrying capacity in the blood); the development of cataracts; and lesions of the respiratory tract (ATSDR, 2003). Humans experience red blood cell hemolysis after naphthalene exposure through oral, inhalation and dermal routes, and appear to be more susceptible to hemolysis than animals (ATSDR, 2003). Naphthalene exposure via the three main routes also results in cataracts in humans based on case and industrial exposure studies. Unfortunately, these industrial studies have not been verified by epidemiological studies, and impurities present in the industrial grade naphthalene may also contribute to cataract formation. Animal studies have also demonstrated a cause and effect relationship between naphthalene and cataracts. Both non-neoplastic and neoplastic respiratory lesions have been associated with naphthalene exposure in mice and rats. An acute human exposure to naphthalene via consumption of mothballs or chips has resulted in several deaths, while sub-lethal acute naphthalene poisoning has resulted in hemolytic anemia and cataracts.

Oral toxicity of 2-methylnaphthalene has been characterized in studies with mice. One study found pulmonary alveolar proteinosis from diets with doses as low as 50.3 mg/kg/day (ATSDR, 2003). A second study of 81-week duration found decreased neutrophils and lymphocyte increases compared to controls.

Inhalation Exposure

Gastrointestinal and neurological symptoms have been reported by a family exposed to high naphthalene indoor air concentrations resulting from excessive use of mothballs (US EPA, 2002). Removal of the mothballs from the home resulted in the cessation of symptoms. A rat study found decreased sensitivity to pain following inhalation exposure to 352 or 525 mg/m^3 2-methylnaphthalene (ATSDR, 2003).

Dermal Exposure

Pulmonary alveolar proteinosis was noted in nearly all female mice administered a mixture of 1- and 2-methylnaphthalene for 30- and 61-week durations (ATSDR, 2003).

Reference Dose for Chronic Oral Exposure (RfD)

Naphthalene

US EPA has developed an RfD for naphthalene of 0.02 mg/kg/day based on a rat study with naphthalene administered in corn oil via gavage (US EPA, 2004a). Parameters examined in the study included: food consumption and body weight, clinical signs of toxicity, hematological parameters, necropsy and histopathological examination of 27 organs in the control and highest dose group at study termination. Decreased body weight was determined to be the most sensitive effect; a decrease in mean body weight of greater than 10% relative to the control group occurred in male rats exposed to 200 mg/kg naphthalene and this value was used for the LOAEL. The NOAEL was 100 mg/kg, which is 71.4 mg/kg/day when adjusted for exposure duration. An uncertainty factor of 3000 was applied to the NOAEL and consisted of: a factor of 10 to account for interspecies extrapolation; a factor of 10 to account for sensitive subpopulations; a factor of 10 to account for the use of a subchronic study to develop a chronic RfD; and a factor of 3 for database deficiencies including the lack of chronic oral and two-generation reproductive studies. The US EPA indicates that confidence in the RfD is low because, although the study was well designed, the database is lacking in chronic oral data and the lack of dose-response data for hemolytic anemia, which is one of the primary potential health hazards associated with human exposure to naphthalene (US EPA, 2004a). As confidence in the database is low, confidence in the RfD is also low.

2-Methylnaphthalene

The RfD for 2-methylnaphthalene is 4E-3 mg/kg/day based on a dietary 81-week study with mice and a critical effect of pulmonary alveolar proteinosis (PAP), a lung disorder in which the alveoli fill with surfactant (US EPA, 2004b). The RfD is based on a benchmark response level of 5% extra risk of the critical effect (BMD_{05}) of 4.7 mg/kg/day and a lower 95% confidence limit of that value ($BMDL_{05}$) of 3.5 mg/kg/day. An uncertainty factor of 1000 has been applied to the BMD_{05}, made up of factors of: 10 for interspecies extrapolation; 10 for protection of sensitive subpopulations; and 10 for database deficiencies. Confidence in the RfD value for 2-methylnaphthalene is reported as being medium for the principle study and low for the database and RfD value (US EPA, 2004b). The principal study was sufficiently large and measured numerous endpoints, but confounding exposure of controls to volatilized 2-methylnaphthalene and 1-methylnaphthalene reduce the overall confidence in the study. The database does not include human exposure, and no animal bioassays are available that focus on developmental, reproductive or neurological effects.

Reference Concentration for Chronic Inhalation Exposure (RfC)

Naphthalene

The US EPA has developed an RfC of 0.003 mg/m^3 for naphthalene based on a chronic mouse inhalation study (US EPA, 2004a). Parameters examined in this study included hematology (limited number of animals only), biomicroscopy and ophthalmoscopic

examinations (limited number of animals at six month intervals) and gross necropsies and histopathological examinations on all animals remaining at study termination. The US EPA (2004) concluded that the observed naphthalene-related effects were caused by reactive oxygenated metabolites formed following absorption of naphthalene rather than direct contact with naphthalene, based on the low water solubility and reactivity of naphthalene. Following US EPA guidance (US EPA, 2004a) for category 3 gases, an RfC was derived by adjusting experimental exposure concentrations for a continuous exposure duration and then converted this dosed to a human equivalent concentration (HEC) by multiplying the experimental concentration adjusted for continuous exposure by the ratio of the mouse-to-human blood/gas partition coefficients. As blood/gas partition coefficients are not available for naphthalene, a default of one was utilized. A NOAEL could not be derived from the study detailed above and a LOAEL (HEC) of 9.3 mg/m^3 was selected based on nasal effects in mice. An uncertainty factor of 3000 was applied to the LOAEL consisting of: a factor of 10 to account for interspecies extrapolation; a factor of 10 to account for sensitive subpopulations; a factor of 10 to extrapolate from a LOAEL to a NOAEL; and a factor of 3 for database deficiencies including the lack of chronic oral and two-generation reproductive studies. The US EPA indicates confidence in the RfC is low to medium; although adequate numbers of mice were used and increased severity in nasal effects was noted with increased exposure, the principle study demonstrated high mortality in the male control group due to fighting and did not measure hematological parameters after 14 days (US EPA, 2004a). The database is lacking in chronic or subchronic inhalation studies in other animals and because there are no reproductive or developmental studies for inhalation exposure. Overall confidence in the RfC is low to medium.

2-Methylnaphthalene

An RfC is unavailable for 2-methylnaphthalene at this time, due to inadequate data (US EPA, 2004b).

Carcinogenic Effects

The US EPA has classified naphthalene as Class C – possible human carcinogen due to inadequate human data via oral or inhalation exposure routes and limited evidence of carcinogenicity in animals. The available human data are inadequate to identify a causal relationship between naphthalene and cancer in humans. The incidence of benign respiratory tumors and one case of carcinoma in female mice provide limited, suggestive evidence that naphthalene may cause cancer. The mechanism by which the respiratory tumors are produced is not known, however, may involve the production of oxygenated reactive metabolites by the cytochrome P-450 system (US EPA, 2004a). Naphthalene has generally produces negative results in genotoxic tests. Quantitative estimates of slope factors or unit risk values are not available at this time.

2-Methylnaphthalene is not classified by the US EPA for carcinogenicity because the data from a single study on mice and the lack of human carcinogenicity data are inadequate to assess human carcinogenic potential (US EPA, 2004b).

Carcinogenic Risk from Oral Exposure
Oral slope factors for naphthalene and 2-methylnaphthalene are not available at this time (US EPA, 2004a and 2004b).

Carcinogenic Risk from Inhalation Exposure
Inhalation slope factors for naphthalene and 2-methylnaphthalene are not available at this time (US EPA, 2004a and 2004b).

Summary

Naphthalene

Oral chronic RfD	0.02 mg/kg/day	weight loss	US EPA, 2004a
Inhalation RfC	0.003 mg/m^3	nasal effects	US EPA, 2004a
Oral Slope Factor	not available at this time		US EPA, 2004a
Inhalation Slope Factor	not available at this time		US EPA, 2004a

2-Methylnaphthalene

Oral chronic RfD	4E-3 mg/kg/day	lung disorder	US EPA, 2004b
Inhalation RfC	not available at this time		US EPA, 2004b
Oral Slope Factor	not available at this time		US EPA, 2004b
Inhalation Slope Factor	not available at this time		US EPA, 2004b

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2003. Toxicological Profile for Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene. Draft for External Review.

United States Environmental Protection Agency (US EPA). 1998. Toxicological Review of Naphthalene.

US EPA. 2002. Health Effects Support Document for Naphthalene. External Review Draft. Prepared by Sciences International, Inc. for Health and Ecological Criteria Division, Office of Water. EPA 822-R-02-031.

US EPA. 2004a. Integrated Risk Information System (IRIS) Summary for Naphthalene. URL: http://www.epa.gov/iris/

US EPA. 2004b. Integrated Risk Information System (IRIS) Summary for 2-Methylnaphthalene. URL: http://www.epa.gov/iris/

NICKEL

Pharmacokinetics

Oral Exposure
Studies examining the absorption of nickel by humans found that nickel sulphate is 40 times more bioavailable if administered in water than in food (ATSDR, 1997). The bioavailability of nickel also increases when administered in a soft drink, but not when given in milk, coffee, tea or orange juice (ATSDR, 1997). Nickel serum levels were found to be elevated in subjects who had not eaten prior to the administration of nickel in drinking water, but this was not the case for those who were administered nickel in food. Food tends to decrease the bioavailability of nickel. Some nickel sensitive individuals were found to have decreasing nickel serum concentrations and increasing nickel urinary concentrations with increased administered nickel concentrations (ATSDR, 1997). This may be an indication that some nickel sensitive individuals can decrease nickel absorption in response to increased nickel intake. Most ingested nickel is excreted via feces, although the nickel absorbed by the gastrointestinal tract is excreted in the urine. In comparison studies of nickel doses administered with food or water, 26% of the dose given in water was eliminated in the urine and 76% in the feces by the fourth day following administration (ATSDR, 1997). In contrast, 2% of the nickel dose administered in food was eliminated in the urine and 102% was eliminated in the feces during the same time period. Nickel can also be eliminated through hair, sweat, milk and skin.

Inhalation Exposure
Following an inhalation exposure, nickel tends to accumulate in the lungs. Absorption from the respiratory tract is dependent upon solubility of the nickel compound. Occupational exposure to nickel results in higher nickel lung burdens than the general population. Nickel-sensitized individuals had similar nickel levels in blood, urine and hair relative to non-sensitive individuals. Inhaled nickel is excreted through the urine. Studies conducted on nickel workers show that nickel urinary excretion increased towards the end of the shift and also towards the end of the workweek, indicating that one fraction is removed quickly, with a second fraction removed slowly. In non-occupationally exposed people, nickel concentrations tend to be highest in lungs, thyroid and adrenal glands, kidney, heart and liver.

Dermal Exposure
No studies were located regarding excretion of nickel in humans or animals after dermal exposure to nickel.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Gastrointestinal effects were reported after workers drank water from a fountain containing nickel sulphate and nickel chloride (ATSDR, 1997). Exposure doses ranged from 7.1 to 35.7 mg/kg. Symptoms included nausea, abdominal pain, vomiting and diarrhea. Neurological effects were also observed in the affected workers. Asthma may occur in a small number of sensitized individuals. However, continued oral exposure to nickel has also been shown to desensitize some individuals and prevent sensitization in other cases (ATSR, 1997). Based on animal studies, a minimal dietary nickel requirement of 50 µg/kg of diet is recommended (ATSDR, 1997). The average dietary nickel intake for the US populations is about 150 to 168 µg/day (70-kg person), so nickel deficiency is not expected to affect the general population (ATSDR, 1997).

Inhalation Exposure
The only data available for chronic nickel inhalation exposure for humans are limited to occupational data. One of the limitations associated with the epidemiological data available is that the workers were exposed to several different forms of nickel as well as other metals and irritant gases at the same time, so frequently the observed effects can not be attributed to a particular type of nickel and in some cases to nickel at all, if other metals were also used in the refining, mining or smelting processes (ATSDR, 1997). Other lifestyle factors, such as smoking, which affect disease outcomes are also not always available, limiting the conclusions that can be drawn. Respiratory effects found in nickel workers included chronic bronchitis, emphysema, and reduced vital capacity. These workers were also exposed to other metals, so it cannot be concluded that nickel is the sole causative agent of the effects observed. Asthma from primary irritation and as the result of dermal sensitization has also been documented amongst nickel workers. Nickel refinery workers with elevated urinary nickel concentrations also showed a significant increase in urinary $ß_2$-microglobulin levels, which is indicative of tubular dysfunction in the kidneys (ATSDR, 1997).

Dermal Exposure

Nickel dermatitis is the most prevalent effect of nickel and occurs in nickel-sensitized individuals (ATSDR, 1997). Nickel sensitization results from extensive contact with nickel-containing material such as jewelry, coins, dental braces, stainless steel etc. Contact dermatitis may also result from occupational exposure. Once an individual has been sensitized to nickel, subsequent exposure (though inhalation, ingestion, or dermal contact) to low levels of nickel may cause a reaction. Populations that are unusually susceptible to nickel are those people already sensitive to nickel due to prolonged contact. Subsequent exposures may result in an allergic reaction. A greater number of women tend to be sensitized to nickel than men and this is believed to be related to the fact that

woman tend to wear more metal jewelry than men. Further study is required to determine whether there is indeed a gender difference in nickel sensitivity. Persons with kidney dysfunction are also likely to be more susceptible to nickel as the primary route of nickel elimination is via the urine.

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for soluble salts of nickel is 2E-2 mg/kg/day (critical effects including decreased body and organ weights) (USEPA, 2004).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC is not available at this time for soluble nickel salts (US EPA, 2004).

Carcinogenic Effects
The US EPA has not assessed soluble nickel salts for carcinogencity.

Nickel refinery dust is classified as Class A – human carcinogen based on human data in which exposure to nickel refinery dust caused lung and nasal tumors in refinery workers in several epidemiological studies, and on animal data in which carcinomas were produced in rats by inhalation and injection. Nickel carbonyl is classified as a Class B2 – probable human carcinogen based on the observation of pulmonary carcinomas and malignant tumors in rats administered nickel carbonyl by inhalation and intravenous injection, respectively. Nickel administered as nickel carbonyl binds to DNA. Nickel subsulfide as Class A – human carcinogen based on increased risks of lung and nasal cancer in humans exposed to nickel refinery dust, most of which was believed to have been nickel subsulfide; increased tumor incidences in animals by several routes of administration in several animal species and strains; and positive results in genotoxicity assays.

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for any nickel compound at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for soluble nickel salts at this time (US EPA, 2004). However the inhalation unit risk for nickel refinery dust is 2.4E-4 per ($\mu g/m^3$) and for nickel subsulphide is 4.8E-4 per ($\mu g/m^3$). Both unit risks are based on epidemiological studies of lung cancer and animal carcinoma data.

Summary

Oral Chronic RfD	2E-2 mg/kg/day	decreased weight	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Unit Risk (Ni refinery dust)	2.4E-4 ($\mu g/m^3$)	lung cancer	US EPA, 2004
Inhalation Unit Risk (Ni subsulphide)	4.8E-4 ($\mu g/m^3$)	lung cancer	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological Profile for Nickel.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Soluble Nickel Salts, Nickel subsulphide, Nickel Refinery Dust and Nickel Carbonyl. URL: http://www.epa.gov/iris/

POLYCYCLIC AROMATIC HYDROCARBONS (PAHS)

Pharmacokinetics

Oral Exposure

The compound type and vehicle of administration may affect absorption of PAHs following oral exposure. In animals, ingested PAHs are taken up by the gastrointestinal tract in fat-soluble compounds, with the relative rate of absorption among the PAH compounds depending on lipophilicity. Oral absorption increases with lipophilic content. Oral absorption of benzo[a]pyrene was estimated to be 40%, with a bioavailability of 7.8-11.5%, in Sprague-Dawley rats infused intraduodenally (ATSDR, 1995). There was no information available on the distribution of PAHs in humans following oral exposure, however, PAHs appear to be widely distributed in tissues of animals following oral exposure. The highest PAH concentrations are found in the small intestine, kidneys, lungs, liver and stomach, with limited placental transfer. The lipophilicity of PAHs enables them to readily penetrate cellular membranes and remain in the body for long periods of time. The metabolism of PAHs forms compounds, which are more water-soluble and therefore, excreted. The structural similarity of PAHs contributes to the similarities in their biotransformation, with metabolism occurring in all tissues and involving several possible pathways. Quantitative data on the excretion of PAHs in humans are lacking. PAHs are eliminated to a large extent within 2 days following low- and high-level oral exposure in rats (ATSDR, 1995).

Inhalation Exposure

Absorption of PAHs in humans following inhalation exposure can be inferred from the presence of urinary metabolites of PAHs in workers exposed to these compounds. Animal studies on inhalation absorption of PAHs are limited to benzo[a]pyrene exposure. Animal studies show that absorption of benzo[a]pyrene via inhalation occurs and may be influenced by carrier particles. Rapid absorption occurs following inhalation exposure of low and high levels of benzo[a]pyrene to rats (ATSDR, 1995). Feces are the major elimination route in animals following inhalation exposure of PAHs. Excretion of benzo[a]pyrene appears to be high following low-level exposure in rats but low in dogs and monkeys (ATSDR, 1995).

Dermal Exposure

Dermal absorption of PAHs appears to be rapid for both humans and animals, although the extent of absorption is variable among these compounds and may be affected by the vehicle used for administration (ATSDR, 1995). Application of 2% crude coal tar to the skin of humans for 8-hour periods on 2 consecutive days yielded evidence of PAH absorption (ATSDR, 1995). Phenanthrene, anthracene, pyrene, and fluoranthene were detected in the blood, but benzo[a]pyrene was not detected. Although PAHs can readily

penetrate the skin, there are few data on distribution to tissues. In a dermal application study in rats, levels of pyrene were highest in the liver, kidneys, and fat with metabolites high in the lung. Following dermal exposure elimination of PAHs occurs rapidly in the urine and feces of guinea pigs and rats.

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Data are limited on toxic effects resulting from human oral exposure to PAHs. Effects in animals include hematological, hepatic, renal, reproductive, developmental, and genotoxic (ATSDR, 1995).

Inhalation Exposure
Statistically significant decreases in ventilatory function and other respiratory symptoms (e.g, breathing problems, chest pains, throat irritation, and cough) occurred following prolonged exposure to PAHs and particulate matter have been found to correlate with employment duration in a rubber factory (ATSDR, 1995). Another study showed that coke oven workers, exposed to high concentrations of atmospheric PAHs had reduced levels of serum immunoglobins. Genotoxic effects have also been revealed in women exposed to burning wood and/or coal.

Dermal Exposure
Dermal application of mixtures of PAHs can cause skin disorders in humans and animals; however, specific effects in humans of individual PAHs (except for benzo[a]pyrene), have not been reported. Adverse dermal effects have been noted in humans following intermediate-duration dermal exposure to benzo[a]pyrene in patients with the preexisting dermal conditions (ATSDR, 1995). Adverse dermal effects have also been observed in animals following both acute- and intermediate-duration dermal exposure to various PAHs. Skin damage caused by sunlight exposure can be potentiated by anthracene, resulting in skin inflammation (ATSDR, 1995).

Carcinogenic Effects
PAHs are have been found to cause cancer in humans and animals, based on occupational studies with workers who were exposed to mixtures containing PAHs from processes including such as coke production, roofing, oil refining, or coal gasification (ATSDR, 1995). Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lungs and skin following inhalation and dermal exposure, respectively (ATSDR, 1995). Certain PAHs have also been shown to induce cancer in animals. The site of tumor induction is influenced by route of administration.

TEFs and Corresponding Oral Slope Factors (Carcinogenic Risk from Oral Exposure)
The US EPA devised a toxic equivalency factor (TEF) approach, similar to that used for polychlorinated dibenzo-p-dioxins (TCDDs), to assess PAHs quantitatively. Data are currently insufficient to calculate slope factors for PAHs other than benzo(a)pyrene (US EPA, 1993). The advantage of using the TEF approach is that it can be used to quantitatively assess the carcinogenicity of mixtures of PAHs. The PAHs have been divided into two classes – carcinogens and noncarcinogens. The carcinogens have been assigned relative potency factors (RPFs) that indicate the carcinogenic potency of each PAH relative to benzo(a)pyrene. Multiplying the RPF of each PAH by the cancer slope factor for benzo(a)pyrene provides an estimated cancer slope factor for each compound. The following table summarizes oral (CSF_o) and inhalation slope (CSF_i) factors used for PAHs in this risk assessment, and is based on WDNR (1997), which provides RPFs for a wide range of PAHs. Modifications to WDNR (1997) inhalation slope factor for benzo(a)pyrene have been made to reflect the current, provisional value derived by US EPA NCEA (3.1 $(mg/kg/day)^{-1}$) (US EPA Region 3, 2003; ORNL, 2004).

COMPOUND	RPF	CSF_O $(MG/KG/DAY)^{-1}$	CSF_I $(MG/KG/DAY)^{-1}$	RFD (MG/KG/DAY)
Acenaphthene	0.001			6E-2
Acenaphthylene	0.001	7.3E-3	3.1E-3	na
Anthracene	0.01			3E-1
Benz[a]anthracene	0.1	7.3E-1	3.1E-1	
Benzo[a]pyrene	1	7.3	3.1*	
Benzo[b]fluoranthene	0.1	7.3E-1	3.1E-1	
Benzo[g,h,i]perylene	0.01	7.3E-2	3.1E-2	na
Benzo[k]fluoranthene	0.01	7.3E-2	3.1E-2	
Chrysene	0.001	7.3E-3	3.1E-3	
Dibenz[a,h]anthracene	1	7.3	3.1	
Fluoranthene	0.001			4E-2
Indeno[1,2,3-cd]pyrene	0.1	7.3E-1	3.1E-1	
2-Methylnaphthalene	0.001			4E-2
Naphthalene	0.001			4E-3
Phenanthrene	0.001	7.3E-3	3.1E-3	na

* The 6.1$(mg/kg/day)^{-1}$ value for benzo(a)pyrene CSF_i was removed from the US EPA Integrated Risk Information System in 1993 and was replaced with the provisional US EPA NCEA value of 3.1 $(mg/kg/day)^{-1}$ for the purpose of this risk assessment.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for PAHs.

Oak Ridge National Laboratories. Risk Assessment Information System (RAIS). 2004. online memo. Toxicity Values. http://risk.lsd.ornl.gov/tox/toxvals.shtml

United States Environmental Protection Agency (US EPA). 1993. Provisional Guidance for Quantitative Risk Assessment of Polycyclic aromatic hydrocarbons. US Environmental Protection Agency, Office of Research and Development, EPA/60/R-93/089. 20p.

US EPA Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

Wisconsin Department of Natural Resources (WDNR). 1997. Soil Cleanup levels for polycyclic aromatic hydrocarbons (PAHs) interim guidance. Bureau for Remediation and Redevelopment. Publication RR-519-97.

PHENANTHRENE

See PAH profile.

2,3,7,8-TCDD

Pharmacokinetics

Oral Exposure
The absorption of 2,3,7,8-TCDD was estimated to be greater than 87% in a human volunteers following ingestion of a single radioactively labeled dose of 1.14E-6 mg/kg 2,3,7,8-TCDD. Absorption of approximately 70-75% of the total dose administered by gavage has been observed in studies with Syrian hamsters and rats. Gastrointestinal absorption may vary depending on the vehicle used (e.g., absorption in the gastrointestinal tract of rats was 50% less from contaminated soil than from corn oil) (ATSDR, 1998). Approximately 90% of the human body burden of 2,3,7,8-TCDD may be distributed to the fatty tissue (ATSDR, 1998). Studies in animals have shown that 2,3,7,8-TCDD distributes preferentially to the liver and adipose tissue.

Studies suggest elimination occurs slowly via metabolism with phase I metabolizing enzymes (oxidation and reductive dechlorination). Conjugation reactions catalyzed by phase II type enzymes, which facilitate excretion by adding more polar groups to the molecule, follow phase I metabolism. 2,3,7,8-TCDD metabolites appear to be readily eliminated, as the metabolites are not generally detected in tissues.

Fecal elimination is the major route of excretion, although excretion in the urine, and expired air has also been reported (ATSDR, 1998). A median half-life of 7.1 years was estimated for 2,3,7,8-TCDD, based on measurement of serum levels, in a small group of Vietnam veterans (ATSDR, 1998). The half-life for elimination of a single oral dose of 1.14E-6 mg/kg 2,3,7,8-TCDD in a human volunteer was calculated to be 5.8 years and approximately 12% of the administered dose was excreted within a few days of administration. The half-life of 2,3,7,8-TCDD is highly variable among different species (e.g., 14 days for the Syrian hamsters, 12-17 days in rats, 94 days in guinea pigs, and 391 in monkeys). 2,3,7,8-TCDD is a lipophilic compound that concentrates in maternal milk and lactation decreases the body burden of these compounds. Several studies have shown that 2,3,7,8-TCDD is readily absorbed from breast milk by nursing infants.

Inhalation Exposure
Quantitative data were unavailable regarding absorption of 2,3,7,8-TCDD in humans following inhalation exposure. Data on levels of 2,3,7,8-TCDD in blood from

populations with above-background exposures (either occupational or accidental) also suggest pulmonary absorption occurs in humans. Systemic effects (cytochrome P-450 induction and hepatic histological alterations) were observed in rats following a single intratracheal treatment of 2,3,7,8-TCDD (ATSDR, 1998). Subsequent analyses of the rates indicated12 to 14% absorption of the administered 2,3,7,8-TCDD dose in the liver. The liver and adipose tissues are the primary tissue stores for 2,3,7,8-TCDD, with 33 and 15% of the applied dose distributing to these respective tissues. In male rats administered a single intratracheal dose of 3.2E-4 mg labeled 2,3,7,8-TCDD/kg, feces was the major route of excretion over a 3-day period (ATSDR, 1998). The cumulative excretion of 26.3% of the administered dose was observed over 3 days following exposure.

Dermal Exposure

No quantitative data were located regarding absorption of 2,3,7,8-TCDDs in humans following dermal exposure. The rate of 2,3,7,8-TCDD penetration of the skin when applied with acetone as vehicle ranged from 1 to 8E-7 mg 2,3,7,8-TCDD/hr-cm^2 using an experimental approach or 6E-9 to1.7E-7 mg/hr-cm^2 with a physiological model approach (ATSDR, 1998). Approximately 15% of the administered dose was detected in the liver of rats, 24 hours following dermal exposure to 2.6E-5 mg of 2,3,7,8-TCDD in methanol (ATSDR, 1998). Dermal absorption of radioactively labeled 2,3,7,8-TCDD in soil was reported to be only 1% of the administered dose during a 24-hour contact period in rats (ATSDR, 1998).

Toxicity

Non-Carcinogenic Effects

Oral Exposure

Data indicate that oral exposure to low levels of 2,3,7,8-TCDD from food (including milk) represents the major route of environmental exposure for the general population. Transfer of 2,3,7,8-TCDD to the fetus can occur across the placenta and, although the amounts may be relatively small, the transfer may have biological significance if it occurs during critical periods of organ formation and development (ATSDR, 1998). The liver is a primary target of 2,3,7,8-TCDD inducing effects that include alterations in metabolism, biochemical changes, and increased liver weight. Immune systems of several men who consumed large amounts of 2,3,7,8-TCDD-contaminated fish from the Baltic Sea were also found to be compromised.

Severe respiratory effects have been observed in rhesus monkeys orally exposed to 2,3,7,8-TCDD (ATSDR, 1998). Cardiovascular effects have also been detected in animals following variable oral exposures to 2,3,7,8-TCDD (ATSDR, 998). One of the major 2,3,7,8-TCDD-induced effects in various animal species is the wasting syndrome and hypophagia (ATSDR, 1998). 2,3,7,8-TCDD was shown to alter endocrine parameters in rodent including decreases in serum T4 (ATSDR, 1998). Developmental effects (e.g., cleft palates, hydronephrosis, impaired development of the reproductive system,

immunotoxicity) were seen in rodents and monkeys exposed orally to 2,3,7,8-TCDD (ATSDR, 1998).

Acute oral exposure studies to 2,3,7,8-TCDD found NOAELs ranging from 5E-6 mg/kg/day in hamsters (gastrointestinal endpoints) to 6 mg/kg/day in mice (immunological endpoints) (ATSDR, 1998). LOAELs for acute oral exposure in mice ranged from 1E-5 mg/kg/day (immunological endpoints) to 1.95 mg/kg/day (renal endpoints). Chronic oral exposure studies to 2,3,7,8-TCDD found NOAELs to range from 1.2E-7 mg/kg/day in rhesus monkeys (reproductive endpoints) to 3E-4 mg/kg/day in mice (several systemic endpoints). LOAELs were from 1.2E-7 mg/kg/day in rhesus monkeys (reproductive endpoints) to 3.6E-4 mg/kg/day in mice (body weight endpoints) (ATSDR, 1998).

Inhalation Exposure

Occupational exposure to 2,3,7,8-TCDD most likely occurs mainly via inhalation of contaminated particles or dust. Effects of acute massive exposure in workers exposed to 2,3,7,8-TCDD in an industrial accident in Germany included bronchitis and laryngitis, a few days after exposure, and hemorrhagic pleuritis, 11 months after exposure (ATSDR, 1998). In an occupationally exposed group, decreased pulmonary function was found in smokers 10 years after the cessation of manufacture of herbicides contaminated with 2,3,7,8-TCDD compared to non-exposed smokers. There is suggestive yet inconclusive evidence of adverse cardiovascular effects in humans exposed to relatively high concentrations of 2,3,7,8-TCDD (e.g., increased deaths from heart and circulatory disease were reported among German workers exposed to 2,3,7,8-TCDD; ATSDR, 1998).

Dermal Exposure

Dermal exposure is most likely through contact with solutions containing 2,3,7,8-TCDD. A study conducted in Missouri on human dermal contact with 2,3,7,8-TCDD-contaminated soil by physical or recreational activities for 6 months at 100 ppb or for 2 years at 20 to 100 ppb resulted in a slight, but statistically significant increase in total white blood cell (WBC) counts (ATSDR, 1998). Simultaneous inhalation or oral intake was not quantified, and a subsequent study on the same study group found no difference in the number of red blood cells, WBCs, or platelets between exposed and nonexposed individuals.

Reference Dose for Chronic Oral Exposure (RfD)

An RfD is not available for 2,3,7,8-TCDD.

Reference Concentration for Chronic Inhalation Exposure (RfC)

An RfC is not available for 2,3,7,8-TCDD.

Carcinogenic Effects
The US EPA classifies 2,3,7,8-TCDD as Class B2 – probable human carcinogen (US EPA, 1997).

Carcinogenic Risk from Oral Exposure
The Health Effects Assessment Summary Table (HEAST) indicates that the oral slope factor for 2,3,7,8-TCDD is 1.5E5 mg/kg/day (US EPA, 1997), based on the occurrence of respiratory system and liver tumors in rats from dietary exposure over ~ 2 years. The oral slope factor value is reported as being under review and subject to change.

Carcinogenic Risk from Inhalation Exposure
The inhalation slope factor for 2,3,7,8-TCDD is 1.16E5 $(mg/kg/day)^{-1}$ based on an estimated unit risk 3.3E-1 $(\mu g/m^3)^{-1}$ provided by the US EPA in 1997 (US EPA, 1997).

Summary

Oral Chronic RfD	not available		US EPA, 1997
Inhalation RfC	not available		US EPA, 1997
Oral Slope Factor	1.5E5 mg/kg/day	liver tumors	US EPA, 1997
Inhalation Slope Factor	1.16E5 $(mg/kg/day)^{-1}$	respiratory system tumors	US EPA, 1997

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1998. Toxicological Profile for Chlorinated Dibenzo-p-dioxins (CDDs).

United States Environmental Protection Agency (US EPA). 1997. Health Effects Assessment Summary Tables (HEAST), FY 1997 Update. EPA-540-R-97-036. Prepared for the Office of Solid Waste and Emergency Response.

THALLIUM

Pharmacokinetics

Oral Exposure
There are limited data that show thallium is absorbed through the gastrointestinal tract in humans, with indirect exposure occurring via mucocilary clearance following inhalation exposure (ATSDR, 1992). Absorption is nearly complete in humans and animals, with accumulation in humans occurring in the scalp, renal papilla, renal cortex, heart and spleen, with lower levels found in the brain (ATSDR, 1992). A radiolabeling study with a terminally ill patient where thallium was administered over 5 days found 0.4% of the administered dose was excreted in the feces and 11% in the urine during a 72-hour collection period, with a total of 15.3% excreted in the urine after 5.5 days (a half-life of 21.7 days was estimated) (ATSDR, 1992).

Inhalation Exposure
No studies were found on the absorption or distribution of thallium in humans or animals following inhalation exposure, although an occupational study in a battery plant found thallium in the urine ranging from = 50 to 236 μg/L (ATSDR, 1992).

Dermal Exposure
No studies were found on the absorption, distribution and excretion of thallium in humans or animals following dermal exposure (ATSDR, 1992).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Effects in humans following oral exposure to thallium include: death due to nerve damage; respiratory system, cardiovascular system, liver, kidney and muscle damage; and possible hair loss (ATSDR, 1992). Lung and nervous system damage was caused following exposure to 54 to 110 mg/kg thallium nitrate. It has also been found that thallium can cross the human placenta, although developmental effects are not well characterized (ATSDR, 1992).

Inhalation Exposure
Few studies were found on the effects of thallium on humans and animals following inhalation exposure; one long-term occupational study found effects to the nervous system including parasthesia, numbness of toes and fingers, “burning feet” and muscle cramps) following long-term occupational exposure, unfortunately 50% of patients had concomitant, unrelated diseases such as diabetes, obesity and alcoholism, which limits the value of the study (ATSDR, 1992). Limited occupational studies find no effects to the cardiovascular and gastrointestinal systems following inhalation exposure to thallium.

Dermal Exposure
No studies were found on the toxicity of thallium to humans or animals following dermal exposure (ATSDR, 1992).

Reference Dose for Chronic Oral Exposure (RfD)
An RfD is not available for thallium on the US EPA IRIS website, however US EPA Region 3 provides an RfD as 7E-5 mg/kg/day (US EPA Region 3, 2003) which is based on the IRIS RfD for thallium sulphate, converted to thallium salt with a molecular weight adjustment (US EPA Region 9, 2002).

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC was not found for thallium.

Carcinogenic Effects
Carcinogenicity information was not found for thallium.

Carcinogenic Risk from Oral Exposure
An oral slope factor was not found for thallium (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor was not found for thallium (US EPA, 2004).

Summary

Oral Chronic RfD	7E-5 mg/kg/day	US EPA Region 3, 2003
Inhalation RfC	not found	US EPA, 2004
Oral Slope Factor	not found	US EPA, 2004
Inhalation Slope Factor	not found	US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1992. Toxicological Profile for Thallium.

United States Environmental Protection Agency (US EPA) Region 9. 2002. Region 9 PRGs Table 2002 Update.

US EPA Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS).
URL: http://www.epa.gov/iris/

TOLUENE

Pharmacokinetics

Oral Exposure
Volunteer and animal studies indicate toluene is readily absorbed from the gastrointestinal tract. Toluene administered via oral exposure is distributed to the adipose tissue, brain and bone marrow, with moderately high concentrations of toluene and its metabolites in the liver and kidney (ATSDR, 2000). Rats orally exposed to 400 mg/kg toluene showed peak concentrations in the blood stream 1.5 hours post-exposure (ATSDR, 2000). Elimination of toluene from oral exposure is similar to that seen in inhalation exposure, with evidence that concomitant uptake of ethanol causes metabolic inhibition (ATSDR, 2000).

Inhalation Exposure
Volunteer and animal studies also indicate toluene is readily absorbed from the respiratory tract. Distribution of toluene administered via inhalation exposure is very similar to that observed after oral exposure (ATSDR, 2000). Humans exposed to 300 mg/m^3 toluene had 2 to 5 μmol/L in the bloodstream within 10 to 15 minutes of exposure, and reached a peak of 6 to 7 μmol/L after 2 hours (ATSDR, 2000). Toluene metabolism has been well characterized, and numerous metabolites are known (ATSDR, 2000). Human and rat studies have found 75 to 80% of inhaled toluene is excreted as hippuric acid in the urine, with the remaining fraction exhaled as unaltered toluene. Toluene (and metabolite) excretion is rapid, with the majority excreted within 12 hours of exposure (ATSDR, 2000). Human and rat studies confirm the majority of toluene is rapidly eliminated from the body, with a smaller portion partitioned in adipose tissue which is more slowly eliminated.

Dermal Exposure
Volunteer and animal studies have shown toluene is also slowly absorbed through the skin, at a rate of 14 to 23 mg/cm^2/hour in human forearm (ATSDR, 2000). No studies have been found that characterize the distribution of toluene following dermal exposure, although one study has shown toluene is eliminated as unaltered toluene in the breath (ATSDR, 2000).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
There are limited studies available on oral exposure to toluene, major toxicological effects include death after 30 minutes (upon ingestion of 625 mg/kg toluene) in humans,

with autopsy-revealed effects including constriction and necrosis of myocardial fibers, swollen liver, congestion and hemorrhage of the lungs and acute tubular kidney necrosis (ATSDR, 2000). Animal data include cardiovascular, hematological, liver and kidney effects from oral exposure of up to 2500 mg/kg/day over 13 weeks or 590 mg/kg/day for 6 months (ATSDR, 2000).

Oral uptake studies with toluene found NOAELs ranging from 22 mg/kg/day in male mice (administered in water) to 2500 mg/kg/day in mice (administered via gavage with oil) (ATSDR, 2000). Oral exposure LOAELs ranged from 4 mg/kg/day (administered in water) in mice (causing impaired motor coordination) to 7300 mg/kg/day (administered via gavage) in rats (corresponding to an LD_{50}) (ATSDR, 2000).

Inhalation Exposure

The most critical effects of toluene from inhalation exposure in humans are on the central nervous system (CNS); these include reversible neurological symptoms (fatigue, headache, decreased manual dexterity) from acute exposure, narcosis with increasing exposure. Chronic solvent abuse can lead to degenerative changes in white matter while chronic occupational exposure can lead to subtle changes in neurological functions, hearing, and color discrimination (ATSDR, 2000). Animal studies concur with human studies, with effects in animals ranging from behavioral changes, hearing loss and subtle changes in brain structure, electrophysiology and chemistry. Birth defects and developmental delays in children born to solvent abusers indicate fetal and developmental effects, while animal studies with rats, mice and rabbits find toluene can retard fetal growth and skeletal development, and alter behavior development in offspring. Additional effects include respiratory tract irritation in humans and animals, and hyperthyroidism and massive bilateral adrenal hemorrhage with severe degeneration and necrosis of the adrenal cortex following chronic solvent abuse.

Inhalation uptake studies with experimental animals found NOAELs for toluene ranging from 4 mg/m^3 following 3 hours exposure in female mice (focusing on immunological effects) to 45,217 mg/m^3 following 8 weeks of exposure, for 5 days/week and 70 minutes/day in male rats (focusing on systemic effects) (ATSDR, 2000). LOAELs ranged from 9 mg/m^3 in female mice (causing increased susceptibility to infections) to 131,883 mg/m^3 in male rats (causing increased delay of initial response of escape and delay to escape) (ATSDR, 2000).

Dermal Exposure

There are few studies on dermal exposure to toluene; although pharmacokinetic data indicate humans and animals are capable of absorbing toluene through the skin, the only reported effects include damage to the skin (caused by lipid removal) in humans, and redness and increased epidermal thickness in guinea pigs following application for 3 days, 3 times/day (ATSDR, 2000).

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for toluene is 0.2 mg/kg/day from a 13-week rat gavage study with a NOAEL of 312 mg/kg (converted to 223 mg/kg/day) and a LOAEL of 625 mg/kg (converted to 446 mg/kg/day) (US EPA, 2004). The total uncertainty factor was 1000; this accounted for interspecies extrapolation, intraspecies variability, subchronic-to-chronic extrapolation and for limited developmental and reproductive toxicity data. Confidence in the oral RfD is reported as high for the quality of the study, and medium for the database and RfD. There was a sufficient sample size in the principle study, although the database is rated as medium as it is supported by a 6-month oral study (which lacks a reproduction study), and relies on sub-chronic tests.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for toluene is 0.4 mg/m^3 based on two principle studies: a human occupational study (with a critical effect neurological impairment), and a 2-year chronic inhalation exposure study in rats (with a critical effect of nasal epithelium degeneration) (US EPA, 2004). For both studies NOAEL values were not determined; the LOAEL for the occupational study was 332 mg/m^3 (adjusted to 119 mg/m^3), and the LOAEL for the rat study was 2261 mg/m^3 (adjusted to a human equivalent concentration of 79 mg/m^3). The uncertainty factor for this RfC is 300 (based on interspecies extrapolation (10), the use of a LOAEL (10), and database deficiencies (3)), and the confidence in the study, database and RfC value is medium based on the use of a LOAEL for both studies, and the lack of long-term data and reproductive/developmental studies in humans.

Carcinogenic Effects
The US EPA has classified toluene as a group D carcinogen – not classifiable as to human carcinogenicity, due to a lack of human data and inadequate data from animal studies (US EPA, 2004).

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for toluene at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for toluene at this time (US EPA, 2004).

Summary

Oral Chronic RfD	0.2 mg/kg/day	liver and kidney effects	US EPA, 2004
Inhalation RfC	0.4 mg/m^3	neurological effects	US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2000. Toxicological Profile for Toluene.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Toluene. URL: http://www.epa.gov/iris/

1,2,4-TRIMETHYLBENZENE, 1,3,5-TRIMETHYLBENZENE

Pharmacokinetics

Oral, Inhalation and Dermal Exposure
Pharmacokinetic information was not found for either trimethylbenzene isomer.

Toxicity

Non-Carcinogenic Effects
Oral, Inhalation and Dermal Exposure
General toxicity information was not found for either trimethylbenzene isomer.

Reference Dose for Chronic Oral Exposure (RfD)
The provisional RfD for 1,2,4-TMB from the EPA-NCEA is 5.0E-2 mg/kg/day, and the provisional RfD for 1,3,5-TMB is the same (US EPA Region 3, 2003). Supporting information is not available.

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC is not available for 1,2,4-TMB or 1,3,5-TMB. The provisional reference dose for inhalation exposure, RfD_i, is 1.70E-3 for both isomers (US EPA Region 3, 2003).

Carcinogenic Effects
Carcinogenicity information for 1,2,4- and 1,3,5-TMB is not available.

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for either TMB isomer.

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for either TMB isomer.

Summary

1,2,4-TMB

Oral Chronic RfD_o	5.0E-2 mg/kg/day	US EPA Region 3, 2003
Inhalation RfD_i	1.7E-3 mg/kg/day	US EPA Region 3, 2003
Oral Slope Factor	not found	
Inhalation Slope Factor	not found	

1,3,5-TMB

Oral Chronic RfD_o	5.0E-2 mg/kg/day	US EPA Region 3, 2003
Inhalation RfD_i	1.7E-3 mg/kg/day	US EPA Region 3, 2003
Oral Slope Factor	not found	
Inhalation Slope Factor	not found	

References

United States Environmental Protection Agency (US EPA) Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist.
URL: http://www.epa.gov/reg3hwmd/risk/index.html

VANADIUM

Pharmacokinetics

Oral Exposure

No oral exposure data have been found on rate and extent of vanadium absorption in humans (ATSDR, 1992). In animals, oral exposure studies have found absorption of vanadium through the gastrointestinal tract is poor. In a rat study, less than 0.1% of vanadium administered intragastrically was detected in the bloodstream 15 minutes after exposure, and less than 1% was detected after 1 hour. Rat distribution studies have found the skeleton is the primary target (0.05%) with 0.01% in the liver, and <0.01% in the kidneys, blood, testis or spleen after 24 hours of acute exposure (ATSDR, 1992). Intermediate exposure studies have found the kidneys are the primary target, followed by bone, liver and muscle in adult rats exposed to 5 or 50 ppm vanadium in water for 3 months (ATSDR, 1992). Vanadium retention in the bones is thought to occur through phosphate displacement, and is greater than in other tissues. No studies were found on the distribution or excretion of vanadium in humans. Animal studies have found vanadium is poorly absorbed in the gastrointestinal tract, with the majority excreted in the urine; 80% of the unabsorbed vanadium was accumulated in the feces after 6 days (ATSDR, 1992). The primary route of absorbed vanadium elimination is through the kidneys (i.e., urinary excretion) in animals (ATSDR, 1992).

Inhalation Exposure

There have been several occupational studies that indicate absorption of vanadium via inhalation exposure occurs as an increase in vanadium in the urine was found in workers exposed to < 2 mg/m^3 vanadium (ATSDR, 1992). Animal studies have found intra-tracheally-administered vanadium in the form of (sodium vanadium) is readily absorbed. In rats, initial pulmonary clearance is rapid (100% of radiolabeled vanadyl chloride was absorbed), with the greatest absorption occurring 5 minutes after administration. Based on rat studies, rapid absorption of vanadium in humans following acute exposure is also possible. The distribution of vanadium in occupational studies have found serum vanadium levels were highest within 24 hours following exposure, and rapidly drops off once exposure is terminated. Studies have shown high levels of vanadium in hair, bone and teeth and low levels of vanadium in kidneys and the liver, with lower amounts found in the brain, heart and milk (ATSDR, 1992). Animal exposure studies have found vanadium is rapidly distributed; after exposure to 0.36 mg/kg vanadium (in the form of vanadium oxychloride), it was detected in all body organs (except the brain) after 15 minutes. The highest concentration was in the lungs, followed by the heart and kidneys, with low levels found in all other organs, maximum concentrations were reached within 4 and 24 hours. Excretion of vanadium following inhalation exposure is mainly via urine in humans and animals. In rats, 40% of radiolabeled vanadium was found in the urine, while

30% remained in the skeleton, and 2 to 7% was in the lungs, liver, kidneys or blood 3 days after exposure (ATSDR, 1992).

Dermal Exposure
No studies were found on the absorption, distribution and excretion of vanadium following dermal exposure (ATSDR, 1992).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Oral exposure to vanadium in humans is not well characterized, although one study on volunteers has found 0.47 to 1.3 mg/kg vanadium (as ammonium vanadyl tartrate) administered in capsule form for 45 to 68 days causes intestinal cramping and diarrhea, although vehicle and compound controls were not used (limiting the quality of the data) (ATSDR, 1992). Rats were also noted to have diarrhea following a 50 ppm dose of vanadium (form unspecified). Rat experiments have also shown mild kidney impairment (exhibited as increased plasma urea and mild histological changes) following 3 months of exposure to sodium metavanadate (at levels up to 10% of the oral LD_{50}), and a slight decrease in body weight.

Inhalation Exposure
Inhalation exposure to vanadium from occupational studies have found minor respiratory irritation as the major form of toxicity; mucus formation, coughing, wheezing, chest pain, runny nose and sore throat are noted as the major (and reversible) effects (ATSDR, 1992). A volunteer study found 0.06 mg/m^3 vanadium (as vanadium pentaoxide) caused coughing and mucus formation 7 to 24 hours following exposure. The major target of vanadium toxicity following inhalation exposure in animals is the respiratory system; monkeys breathing 2.8 mg/m^3 vanadium (as vanadium pentaoxide) for 6 hours showed increased pulmonary resistance 1 day after exposure, with a dramatic increase in polymorphonuclear leucocytes in bronchioalveolar fluid. Workers chronically exposed to vanadium dust demonstrated moderate eye irritation.

Dermal Exposure
No studies were found on the toxicity of vanadium through dermal exposure (ATSDR, 1992).

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for vanadium pentaoxide (V_2O_5) is 9E-3 mg/kg/day based on a NOAEL of 17.85 ppm (adjusted to 0.89 mg/kg/day) (US EPA, 2004). This value is based on a chronic oral study in rats, with decreased hair cystine content as the critical effect. A total uncertainty factor of 100 is applied; a factor of 10 was applied for interspecies extrapolation and a factor of 10 to protect sensitive populations. Confidence in the oral

RfD for vanadium pentaoxide is reported as low for the quality of the study, database and RfD value based on the scarcity of data available (US EPA, 2004).

US EPA NCEA has developed a provisional oral reference dose for vanadium of 3E-4 mg/kg/day (US EPA Region 3, 2003) and this value is used in this risk assessment.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for vanadium in the form of vanadium pentaoxide is unavailable at this time (US EPA, 2004).

Carcinogenic Effects
Vanadium in the form of vanadium pentaoxide has been approved for carcinogenicity testing by the NTP as of 1985; no classification is currently available (US EPA, 2004). No studies have been found that evaluate the carcinogenicity of vanadium in any form, or by any exposure route (ATSDR, 1992).

Carcinogenic Risk from Oral Exposure
There is no inhalation slope factor available for vanadium as vanadium pentaoxide (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
There is no inhalation slope factor available for vanadium pentaoxide (US EPA, 2004).

Summary

Oral Chronic RfD (V)	3E-4 mg/kg/day		US EPA Region 3, 2003
Oral Chronic RfD (V_2O_5)	9E-3 mg/kg/day	NOAEL	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1992. Toxicological Profile for Vanadium.

United States Environmental Protection Agency (US EPA) Region 3. 2003. Risk Based Concentration Table. Originally developed by Roy L. Smith, Ph.D., Toxicologist, revised 10/15/2003 by Jennifer Hubbard, toxicologist. URL: http://www.epa.gov/reg3hwmd/risk/index.html

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Vanadium pentaoxide.

VINYL CHLORIDE

Pharmacokinetics

Oral Exposure
There is no information available regarding absorption of vinyl chloride following oral exposure and limited information is available on the distribution of vinyl chloride in human systems (ATSDR, 1997). Animal data have been used to develop physiologically-based pharmacokinetic (PBPK) models that delineate partitioning coefficients for various compartments in the body. Vinyl chloride is metabolized by cytochrome P-450 monoxygenases as determined by human liver specimens (ATSDR, 1997). Metabolism of the absorbed vinyl chloride allows for continued absorption after initial uptake. Human data indicate that exhalation of unmetabolized vinyl chloride is not an important elimination pathway at low vinyl chloride concentrations.

Inhalation Exposure
Inhalation absorption occurs very rapidly in humans as shown by a group of volunteers who were exposed to four different concentrations of vinyl chloride (7.4, 13, 30 and 60 mg/m^3) for 6 hours by gas mask (ATSDR, 1997). An average retention of 42 % was estimated by measuring the difference between the inhaled and exhaled concentrations. The percentage of vinyl chloride retained was independent of the concentration inhaled and individual variations were noted. The study concluded the major metabolic pathway for vinyl chloride is not saturable, as retention did not change with increased vinyl chloride concentration.

Dermal Exposure
There is no information available regarding absorption of vinyl chloride following dermal exposure (ATSDR, 1997).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
No studies were located regarding systemic effects oral exposure to vinyl chloride in humans. Chronic duration oral exposure of rats to vinyl chloride showed decreased blood clotting time, increased incidence of basophilic foci of cellular alteration, hepatocellular alteration, and increased thickness, moisture content, and collagen content of the skin (ATSDR 1997).

Inhalation Exposure
Non-carcinogenic toxicity associated with vinyl chloride inhalation exposure in the workplace include gastrointestinal effects and Raynaud's Syndrome. Workers exposed to vinyl chloride reported symptoms of nausea and loss of appetite. Raynaud's Syndrome is a vascular condition that causes fingers to become white and numb and is caused by thickening of the walls in the digital arteries (ATSDR, 1997). Raynaud's Syndrome is

caused by exposure to very high levels of vinyl chloride and occurs in only a small percentage of workers, however, the incidence of the disease was significantly higher in workers exposed to vinyl chloride than those who were not exposed. Dizziness and nausea were reported by workers exposed to high levels of vinyl chloride (10,225 to 51,125 mg/m^3) for three minutes twice a day, for a period of three days (ATSDR, 1997). Epidemiological studies of workers exposed to vinyl chloride via inhalation have identified respiratory, gastrointestinal, hepatic, renal and nervous system effects (ATSDR, 1997, US EPA, 2000). Some of the epidemiological studies did not account for confounding factors such as smoking and concomitant exposure to PVC resins, limiting the usefulness of these data.

Dermal Exposure
Dermal exposure to vinyl chloride may occur when it is released from pressurized containers, however dermal effects related to this exposure may be the result of the rapidly evaporating liquid on the skin (ATSDR, 1997). Effects may be due to tissue freezing rather than vinyl chloride toxicity. A man who had liquid vinyl chloride sprayed on his hands reported numbness followed by second-degree burns and finely marked erythema and edema (ATSDR, 1997).

Reference Dose for Chronic Oral Exposure (RfD)
The reference dose for chronic oral exposure (RfD) is 3E-3 (mg/kg/day) based on liver cell polymorphism in rat feeding studies (US EPA, 2004). Vinyl chloride was incorporated into the diet of Wistar rats, at bioavailable doses of 0, 0.014, 0.13, or 1.3 mg/kg/day for a lifetime (US EPA, 2004). A variety of lesions were observed histologically at the highest dose level of 1.3 mg/kg/day. The LOAEL and NOAEL values were determined to be 1.3 mg/kg/day and 0.13 mg/kg/day, respectively. An uncertainty factor of 30 to derive the RfD from the adjusted NOAEL (0.09 mg/kg/day; human equivalent dose) and includes factors for protection of sensitive human subpopulations (10) and interspecies extrapolation (3). The overall confidence in this RfD assessment is medium.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The chronic inhalation exposure reference concentration is 1E-1 mg/m^3 and is based on the same liver cell polymorphism in rat chronic feeding studies mentioned in the RfD section and route-to-route extrapolation using PBPK models (US EPA, 2004). Route-to-route extrapolation was justified in this case because the mode of action is the same regardless of the exposure pathway (i.e., inhalation or oral ingestion). An uncertainty factor of 30 was applied to account for protection of sensitive human subpopulations (10) and for interspecies extrapolation (3). The overall confidence in this RfD assessment is medium

Carcinogenic Effects
Vinyl chloride is classified as a Class A carcinogen – known human carcinogen by oral and inhalation exposure routes based on a weight-of-evidence approach using numerous studies (US EPA, 2000). The weight-of-evidence determination included evidence such as: efficient absorption of vinyl chloride from all exposure routes and rapid distribution

throughout the body; consistent evidence in human occupational inhalation exposure causes liver angiosarcoma; consistent evidence of carcinogenicity in animals via oral and inhalation routes of exposure; and sufficient evidence that vinyl chloride is mutagenic. Liver angiosarcomas are the predominant form of tumor found in workers that were occupationally exposed to vinyl chloride. Other forms of cancer such as hepatocellular carcinomas, brain soft tissue and central nervous system cancers, hematopoetic and lymphatic cancers and lung cancer have also been reported, but the association between these cancers and vinyl chloride exposure is much weaker than that for liver angiosarcomas. Several partial lifetime exposure animal studies have indicated that the lifetime cancer risk may depend on the age at which the exposure occurs (US EPA, 2000). The animal studies also show that cancer incidence increases with increased exposure duration and that incidence decreases with increasing age of initial exposure. The US EPA indicates that while the animal studies demonstrate an increased susceptibility when the initial exposure occurs at an early age, the animals used in the study were near adulthood at the beginning of the study.

Carcinogenic Risk from Oral Exposure

The US EPA calculated oral cancer risks based on evidence of combined angiosarcomas, hepatocellular carcinomas and neoplastic nodules in female rats. Two methods were used to develop the oral cancer slope factors for humans; the linearized multistage model (LMS) and the dose associated with a lifetime cancer risk of 10% (LED). The oral slope factors for vinyl chloride developed by these two methods for continuous lifetime exposure during beginning in adulthood are 7.2E-1 $(mg/kg/day)^{-1}$ (LMS) and 7.5E-1 $(mg/kg/day)^{-1}$ (LED). The US EPA recommends the addition of a two-fold uncertainty factor if the exposure begins early in life.

Carcinogenic Risk from Inhalation Exposure

Inhalation cancer risks developed by the US EPA were based on the incidence of angiosarcoma, angioma, hepatoma or neoplastic nodules in female rats (US EPA, 2000). The LMS and LED approaches were also used to develop unit risk values for inhalation exposure to vinyl chloride. Unit risk values have been developed for continuous lifetime exposures during adulthood and continuous lifetime exposure from birth. The continuous lifetime exposure from birth was calculated by applying an uncertainty factor of 2 to the adult values. The inhalation unit risk for vinyl chloride developed by these two methods for continuous lifetime exposure during beginning in adulthood is 4.4E-9 $(mg/m^3)^{-1}$ (LMS and LED). The inhalation unit risk value for continuous lifetime exposure from birth is 8.8E-9 $(mg/m^3)^{-1}$ (US EPA, 2004).

Summary

Oral Chronic RfD	3E-3 mg/kg/day		US EPA, 2004
Inhalation RfC	1E-1 mg/m^3		US EPA, 2004
Oral Slope Factor (LMS)[1]	7.2E-1 $(mg/kg/day)^{-1}$	numerous cancers	US EPA, 2004
Oral Slope Factor (LED)[1*]	7.5E-1 $(mg/kg/day)^{-1}$	numerous cancers	US EPA, 2004
Oral Slope Factor (LMS)[2]	1.4 $(mg/kg/day)^{-1}$	numerous cancers	US EPA, 2004
Oral Slope Factor (LED)[2*]	1.5 $(mg/kg/day)^{-1}$	numerous cancers	US EPA, 2004
Inhalation Unit Risk[1*]	4.4E-9 $(mg/m^3)^{-1}$	numerous cancers	US EPA, 2004
Inhalation Unit Risk[2*]	8.8E-9 $(mg/m^3)^{-1}$	numerous cancers	US EPA, 2004

[1]Values are for adult continuous lifetime exposure; [1*]used for adult receptors in risk assessment
[2]Values are for continuous lifetime exposure from birth; [*2] used for combined receptors in risk assessment

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological Profile for Vinyl Chloride.

United States Environmental Protection Agency (US EPA). 2000. Toxicological Review of Vinyl Chloride: In Support of Summary Information on the Integrated Risk Information System (IRIS).

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Vinyl Chloride. URL: http://www.epa.gov/iris/

XYLENES (M,P-XYLENE, O-XYLENE)

Pharmacokinetics

Oral Exposure

Xylenes are well absorbed by the oral pathway; almost complete absorption of xylenes following oral exposure was observed in rats, with peak concentrations measured within 20 minutes. Xylenes bind quickly to blood serum proteins (90%) and distribute rapidly into the systemic circulation (ATSDR, 1995). Xylene is then distributed to tissues and accumulates in adipose tissue (5 to 10% of the absorbed dose) due to its high lipophilicity (ATSDR, 1995). The half-life for elimination of xylene from subcutaneous fat is estimated at 7 hours in the rat and greater than 40 hours in humans, indicating accumulation may be possible (US EPA, 1994). *p*-Xylene and *o*-xylene have been shown to cross the placenta with distribution in the amniotic fluid and embryonic and fetal tissues. The level detected in fetal tissues (brain, liver, lung, and kidney), which are low in lipids, was only 2% of that detected in the maternal brain tissue, which contains large amounts of lipids (ATSDR, 1995). Metabolism of xylene in humans occurs primarily by the oxidation of a side-chain methyl group by mixed-function oxidases in the liver to methylbenzoic acids. The elimination half-life of *m*-xylene from subcutaneous adipose tissue has been estimated to be 58 hours in humans (US EPA, 1994). Limited information is available on the elimination of metabolites following oral exposure in humans.

Inhalation Exposure

Xylenes are also well absorbed by the inhalation pathway. Evidence for absorption of xylene in humans following inhalation exposure is provided by the observation that urine metabolites increase in proportion to inhalation exposure (ATSDR, 1995). Several studies with humans exposed by inhalation to xylene at concentrations of 100-1300 mg/m^3 have shown that approximately 50-70% of the xylene present in inspired air is retained by the lungs, regardless of the isomer or mixture used (US EPA, 1994). Radiolabeling studies found *m*-xylene in lungs, liver, kidney, brain, and adipose tissue of mice after a 10-minute inhalation exposure. A volunteer inhalation exposure study where volunteers were exposed to purified xylene isomers at concentrations of 3,777 or 7,555 mg/m^3 for 8 hours found major metabolites present in urine (85-95%). Elimination of *m*-xylene in humans appears to be triphasic following inhalation exposure; based on the rate of elimination of *m*-xylene in expired air, the half-life was 0.8 hours for the initial phase, 7.7 hours for the intermediate phase, and 17.7 hours for the slowest elimination phase (US EPA, 1994).

Dermal Exposure

Xylenes are well absorbed by dermal pathway, although absorption is minor compared to other routes and may occur via exposure to vapors as well as direct contact with xylene solvents. Dermal absorption at a rate of 9.6 mg/cm^2/hour has been reported following

application to the skin of the human forearm (US EPA, 1994). The major route of excretion in rats following dermal application of *m*-xylene was via expired air (62%) and urine (43%) (US EPA, 1994).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
A human autopsy study has found the cause of death following ingestion of a large quantity of xylene was respiratory failure accompanied by pulmonary congestion and edema (ATSDR, 1995). Accidental ingestion of small quantities of a paint thinner containing 90% xylene has resulted in toxic hepatitis (US EPA, 1994). Gavage or diet studies using mixed xylenes with laboratory animals have found decreased body weight gain, hyperactivity, shallow and labored breathing, increased liver and kidney weights, and several neurological and developmental effects. Rib anomalies and cleft palate occurred in mouse fetuses following maternal oral exposure of 2060 mg/kg/day of mixed xylenes (ATSDR, 1995).

Inhalation Exposure
In humans, inhalation exposure to mixed xylenes and *p*-xylene has been associated with irritation of the nose and throat. Chronic occupational exposure of workers to an unspecified concentration of vapors of mixed xylene has also been associated with labored breathing and impaired pulmonary function (ATSDR, 1995). Gastrointestinal symptoms (e.g., nausea, vomiting, and gastric discomfort) have also been noted in workers exposed to xylene vapors. Occupational exposure to xylene vapor over a period of 1.5 to 18 years has been associated with headache, EKG abnormalities, altered memory, and confusion.

Dermal Exposure
Case studies of painters report dryness of the throat, decreased pulmonary function, flushing, chest pains, gastric discomfort and palpitations resulting from chronic dermal exposure to xylene (ATSDR, 1995). Hand immersion studies with *m*-xylene have shown transient irritation, redness, dryness, and scaling of the skin (ATSDR, 1995). Repeated dermal exposure to xylenes may cause drying and defatting of the skin leading to dermatitis in humans.

Reference Dose for Chronic Oral Exposure (RfD)
The oral RfD for mixed xylenes is 0.2 mg/kg/day based on a 2-year, 5 day/week chronic gavage bioassay performed on rats with decreases in body weight and mortality as endpoints (US EPA, 2004). An uncertainty factor of 1000 reflects 10 for interspecies variability, 10 for protection of sensitive sub-populations, and 10 to account for database uncertainty (US EPA, 2004). Confidence in the study, database and RfD are reported as medium.

Reference Concentration for Chronic Inhalation Exposure (RfC)
The RfC for mixed xylenes is 0.1 mg/m^3 based on a subchronic inhalation study in male rats focusing on impairment of motor coordination as a critical effect (US EPA, 2004). An uncertainty factor of 300 was applied to the NOAEL to derive the RfC. The uncertainty factor consists of a (1) factor of 10 to address intraspecies uncertainty; (2) a factor of 3 to account for interspecies differences; and a factor of 3 for the use of a default $NOAEL_{[HEC]}$ with dosimetric adjustments used to calculate a human equivalent concentration (HEC). Confidence in the study, database and RfC are reported as medium.

Carcinogenic Effects
Xylene is classified as Class D – not classifiable as to human carcinogenicity based on the results of studies in rats and mice that did not demonstrate a significant increase in tumors after oral exposure to xylene mixture (US EPA, 2004). Associations between occupational exposure to xylenes and increased risk of leukemia, non-Hodgkin's lymphoma, and cancer of the rectum, colon, or nervous system have been reported (US EPA, 2004). However, small sample sizes, a lack of quantified exposure concentrations, and/or concomitant exposures to other solvents limit the usefulness of these studies.

Carcinogenic Risk from Oral Exposure
An oral slope factor for xylenes is not available at this time (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor for xylenes is not available at this time (US EPA, 2004).

Summary

Oral Chronic RfD*	0.2 mg/kg/day	body weight and mortality	US EPA, 2004
Inhalation RfC*	0.1 mg/m^3	impaired motor skills	US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

*Note: These values apply to mixed xylenes

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Xylenes.

United States Environmental Protection Agency (US EPA). 1994. Toxicity Summary for Xylenes. Risk Assessment Information System. URL: http://risk.lsd.ornl.gov/tox/profiles/xylene_c.shtml

US EPA. 2004. Integrated Risk Information System (IRIS) Summary for Xylenes. URL: http://www.epa.gov/iris/

ZINC

Pharmacokinetics

Oral Exposure
The pharmacokinetics of zinc following oral exposure are well characterized in humans, as it is an essential nutrient and one of the most abundant trace metals in the human body (ATSDR, 2003). Absorption through the duodenum and intestine is homeostatically regulated and under normal physiological conditions, 20 to 30% of ingested zinc is absorbed through passive diffusion and a carrier-mediated process. Zinc content is highest in the muscle, bone, gastrointestinal tract, kidneys, brain, skin, lungs, heart and pancreas (ATSDR, 2003). The majority of zinc is excreted via feces and also via urine, minor routes are through saliva secretion, hair loss and sweat.

Inhalation Exposure
There is limited information available on the absorption, distribution and excretion of zinc following inhalation exposure in humans and animals, although studies have found increased levels of zinc in the blood and urine after inhalation exposure (ATSDR, 2003). The absorption of zinc through the lungs is dependent on the particle size and solubility of the zinc compound, and one occupational study has found elevated zinc in urine following exposure, suggesting that urine is a primary route of excretion.

Dermal Exposure
There is limited information available on the absorption, distribution and excretion of zinc following dermal exposure in humans and animals, although studies have found increased levels of zinc in the blood and urine after exposure to the skin (ATSDR, 2003). No studies were found on the excretion of zinc following dermal exposure in humans or animals (ATSDR, 2003).

Toxicity

Non-Carcinogenic Effects
Oral Exposure
Effects of oral exposure to zinc in humans include gastronomical effects, hematological effects, impaired immune and inflammatory responses following high doses; and neurological effects following ingestion of metallic zinc (causing lethargy, light-headedness, staggering and difficulty in writing) (ATSDR, 2003).

Inhalation Exposure
Effects of inhalation exposure to zinc in humans include: metal fume fever (from zinc oxides); damage to the mucous membranes and dyspnea, cough, pleuritic chest pain, respiratory tract irritation (from zinc chloride); nausea (from zinc oxide and chloride fumes); and various immunological effects (from zinc oxide) (ATSDR, 2003).

Dermal Exposure
The effects of dermal exposure to zinc in humans include: anemia and decreased numbers of platelets (following exposure to zinc chloride solutions); general skin irritation following exposure to zinc chloride; and eye damage following direct eye exposure to a paste containing 30% zinc chloride (ATSDR, 2003).

Reference Dose for Chronic Oral Exposure (RfD)
The RfD for zinc is 3E-1 mg/kg/day based on a human diet supplement study which found 47% decrease in the blood enzyme, erythrocyte superoxide dismutase in adult females after 10-weeks exposure (US EPA, 2004). A NOAEL was not determined, but the LOAEL was 59.72 mg/day (converted to 1.0 mg/kg/day, based on a 60kg body weight for females). An uncertainty factor of 3 was applied to account for a LOAEL derived from a moderate-exposure duration study (using a sensitive sub-population), and the fact zinc is an essential nutrient (US EPA, 2004). Confidence in the RfD is reported as medium for the study, database and RfD value.

Reference Concentration for Chronic Inhalation Exposure (RfC)
An RfC for zinc is unavailable at this time (US EPA, 2004).

Carcinogenic Effects
Zinc is classified as Class D – not classifiable as to human carcinogenicity based on inadequate evidence in humans and animals (US EPA, 2004).

Carcinogenic Risk from Oral Exposure
An oral slope factor is not available for zinc (US EPA, 2004).

Carcinogenic Risk from Inhalation Exposure
An inhalation slope factor is not available for zinc (US EPA, 2004).

Summary

Oral Chronic RfD	3E-1 mg/kg/day	blood enzyme decrease	US EPA, 2004
Inhalation RfC	not available at this time		US EPA, 2004
Oral Slope Factor	not available at this time		US EPA, 2004
Inhalation Slope Factor	not available at this time		US EPA, 2004

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2003. Draft for Public Comment, Toxicological Profile for Zinc.

United States Environmental Protection Agency (US EPA). 2004. Integrated Risk Information System (IRIS) Summary for Zinc and Compounds. URL: http://www.epa.gov/iris/