Appendix C.9

Toxicity Profiles for COPCs

VOLATILE

Acetone

Acetone is an organic solvent with a wide variety of uses in industry, the laboratory and home. It is produced in large quantities and may be released to the environment as stack emissions, fugitive emissions and in waste water in its production and use as a chemical intermediate and solvent. Due to it's volatile nature, most acetone used in solvents will ultimately be released into the air. In the atmosphere, acetone will be lost by photolysis and reaction with photochemically-produced hydroxyl radicals. Half-life estimates average 22 days and are shorter in the summer than winter. If released on soil, acetone will both volatilize and leach into the ground. If released to water, it will also be lost due to volatilization (half-life of 20 hours). Bioconcentration in aquatic organisms and adsorption to sediment should not be significant. (HSDB, 1995).

Occupational exposure to acetone will be via dermal contact and inhalation of the vapor. It is highly volatile and rapidly absorbed by the respiratory system. Small quantities may be absorbed through the skin. The general population is exposed to acetone in the atmosphere from sources such as auto exhaust, solvents, tobacco smoke and fireplaces, as well as dermal contact with acetone-containing consumer products. Because of its solubility in water, acetone is readily absorbed into the bloodstream and transported rapidly throughout the body (HSDB, 1995). Excretion is rapid for 8 hours after a single oral does but was not complete in 24 hours. The ratio of excretion was approximately 40-70% in breath, 15-30% in urine and 10% through skin (Clayton and Clayton, 1981).

Acute human exposure to high levels of acetone produces central nervous system depression and unconsciousness. Prolonged exposure may produce irritation of the respiratory tract, coughing, headache, drowsiness, loss of coordination and in severe cases, come (Clement Associates, 1985). Inhalation of 2000 ppm is fatal upon brief exposure (Arena, 1974). Prolonged or repeated dermal exposure causes skin irritation or contact dermatitis (HSDB, 1995). Other common symptoms associated with acetone exposure include bronchitis, gastritis, pharyngitis and conjunctivitis. Long-term exposure of rates to low levels of acetone produces increases in liver and kidney weights, as well as changes in red blood cell counts (HSDB, 1995).

Acetone significantly reduced the percentage of hatchability in developing chick embryos and caused a high embryonic mortality during the first week of incubation (Ameenuddin and Sunde, 1984). However, no adverse effects were noted in cultured rat embryos exposed to 0.1% acetone.

Acetone has not been tested in a carcinogenicity bioassay, but gave negative results in a skin painting study (Clement Associates, 1985). Acetone was not mutagenic in the Ames assay (Clement Associates, 1985) or in sister chromatid exchange assays (HSDB, 1995). No information is available on the carcinogenic effects of acetone in humane. Acetone is classified as a group D carcinogen.

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Benzene

Benzene, also known as benzol, is a colorless liquid with a sweet odor. Benzene evaporates into air very quickly and dissolves slightly in water. Benzene is highly flammable. Benzene is made mostly from petroleum sources. Because of its wide use, benzene ranks in the top 20 in production volume for chemicals produced in the United States. Various industries use benzene to make other chemicals, such as styrene (for Styrofoam and other plastics), cumene (for various resins), and cyclohexane (for nylon and synthetic fibers). Benzene is also used for the manufacturing of some types of rubbers, lubricants, dyes, detergents, drugs, and pesticides. Natural sources of benzene, which include volcanoes and forest fires, also contribute to the presence of benzene in the environment. Benzene is also a part of crude oil and gasoline and cigarette smoke. Exposure to benzene can occur via inhalation, ingestion, especially of contaminated drinking water, and dermal contact (as in contact with liquid benzene found in gasoline.) (ATSDR, 1997)

Benzene is readily absorbed by both test animals and humans from inhalation, oral, and dermal exposures (IRIS, 2003). Once in the bloodstream, benzene is distributed throughout the body, with the concentration in any one compartment dependent on the degree of perfusion of tissues by blood. Since benzene is lipid-soluble, it accumulates in fat, but the rate of accumulation is slow since fat is poorly perfused. The metabolites of benzene are responsible for its toxic effects. These include phenol (which is either formed via an unstable benzene oxide precursor or directly from benzene), catechol, hydroquinone and conjugated phenolic compounds. The primary site of benzene metabolism is the liver via the cytochrome P450 mixed function oxidase system. Some benzene metabolism may also occur in the bone marrow via the same enzyme system. Benzene is excreted either unchanged from the lungs or as metabolites in the urine (ATSDR, 1997).

Benzene targets its effects on the hemopoietic, immune and nervous systems (ATSDR, 1997, USEPA, 2002). Exposure to benzene has produced irritation of the skin, eyes and upper respiratory tract. Acute exposure has produced central nervous system depression, headache, dizziness, nausea, convulsions, coma and death at extremely high concentrations (Sittig, 1981). Health effects in humans have been reported starting as low as 50 ppm via inhalation. Twenty-five ppm for 6 hrs had no obvious effects though benzene was detected in blood (Sandmeyer, 1981). Early autopsy reports found benzene-induced hemorrhages of the brain, pericardium, urinary tract, mucous membranes

and skin (Sittig, 1981). Chronic exposure to benzene produces blood changes involving an initial increase in levels of erythrocytes, leukocytes and thrombocytes, followed by aplastic anemia indicated by anemia, leukopenia and thrombocytopenia (Sittig, 1981).

The following effects have been produced experimentally in laboratory animals, following exposure to benzene: decreased leukocyte and/or erythrocyte counts, reduction in cellular immunity and bone marrow depression (reduced number of granulopoietic stem cells). Animal studies do not indicate that benzene is teratogenic, but the following fetotoxic effects have been found: reduced fetal weight, altered fetal hematopoiesis, fetal skeletal variations and increased resorptions in pregnant exposed animals. In addition, benzene has produced histopathological changes in ovaries and testes of test animals (ATSDR, 1997).

The RfD for benzene is based on route-to-route extrapolation of the results of benchmark dose (BMD) modeling of the absolute lymphocyte count (ALC) data from the occupational epidemiologic study by Rothman et al. (1996), in which workers were exposed to benzene by inhalation. The RfD is based upon a 95% lower bound benchmark concentration of 8.2 mg/m^3 which was then converted to an equivalent oral dose of 1.2E+0 mg/kg-d which was divided by an uncertainty factor of 300 (3 for effect-level extrapolation, 10 for intraspecies differences (human variability), 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies) to arrive at a chronic RfD for benzene of 4E-03 mg/kg-day (IRIS, 2003).

The RfC for benzene is based on the results of benchmark dose (BMD) modeling of the absolute lymphocyte count (ALC) data from the occupational epidemiologic study by Rothman et al. (1996), in which workers were exposed to benzene by inhalation. The RfD is based upon a 95% lower bound benchmark concentration of 8.2 mg/m^3, which was divided by an uncertainty factor of 300 (3 for effect-level extrapolation, 10 for intraspecies differences (human variability), 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies) to arrive at a chronic RfC for benzene of 3E-02 mg/m^3 (IRIS, 2003).

Benzene and its metabolites have been shown to be mutagenic in a number of in vitro and in vivo studies. Genotoxic effects produced experimentally include structural and numerical chromosome aberrations in humans, animals and cell cultures, and sister chromatid exchanges and micronuclei in vivo animal studies. Benzene exposure has been found to produce an increase in the number of chromosome aberrations associated with myelotoxicity (Sittig, 1981). In addition, sperm head abnormalities, inhibition of DNA and RNA synthesis, DNA binding and interference with cell cycle progression have been shown in vitro studies (ATSDR, 1997).

Epidemiologic studies and case studies provide clear evidence of a causal association between exposure to benzene and acute nonlymphocytic leukemia (ANLL) and also suggest evidence for chronic nonlymphocytic leukemia (CNLL) and chronic lymphocytic leukemia (CLL). Other neoplastic conditions that are associated with an increased risk in humans are hematologic neoplasms, blood disorders such as preleukemia and aplastic anemia, Hodgkin's lymphoma, and myelodysplastic syndrome (MDS). These human data are supported by animal studies. The experimental animal data add to the argument that exposure to benzene increases the risk of cancer in multiple species at multiple organ sites (hematopoietic, oral and nasal, liver,

forestomach, preputial gland, lung, ovary, and mammary gland) (IRIS, 2003). It is likely that these responses are due to interactions of the metabolites of benzene with DNA (Ross, 1996; Latriano et al., 1986). Recent evidence supports the viewpoint that there are likely multiple mechanistic pathways leading to cancer and, in particular, to leukemogenesis from exposure to benzene (Smith, 1996).

Benzene is classified as a "known" human carcinogen (Category A) under the Risk Assessment Guidelines of 1986. Under the proposed revised Carcinogen Risk Assessment Guidelines (U.S. EPA, 1996), benzene is characterized as a known human carcinogen for all routes of exposure based upon convincing human evidence as well as supporting evidence from animal studies. (U.S. EPA, 1979, 1985, 1998; ATSDR, 1997). The oral slope factor for benzene is reported as a range, 1.5 x 10^{-2} to 5.5 x 10^{-2} per (mg/kg)/day. The quantitative oral unit risk estimate is an extrapolation from the known inhalation dose-response to the potential oral route of exposure. The inhalation risk estimate is reported as a range, from 2.2 × 10^{-6} to 7.8 × 10^{-6} per µg/m^3. No relevant data exist in the published literature for oral absorption of benzene in humans. Inhalation absorption is assumed to be about 50% while that of oral is selected as 100% based upon a review of the relevant human and animal literature (U.S. EPA, 1999). Absorption of benzene via the dermal route of exposure is usually less than 1% of the applied dose and therefore it is not considered to contribute significantly the oral risk estimation.

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Bromomethane

Bromomethane (also called methyl bromide) is a colorless gas without much smell**.** Some bromomethane is formed in the ocean, probably by algae or kelp. However, most is made by humans to kill various pests (rats, insects, fungus, etc.) that might be present in homes, foods, or soil. Some bromomethane is also used to make other chemicals (ATSDR, 1992).

There is limited information regarding the absorption of Bromomethane in humans or animals. Medinsky et al. (1984) has shown that at least 97% of a single oral dose was absorbed from the gastrointestinal tract in rats. There is limited information regarding the distribution of chlorodibromomethane after exposure. Data seems to indicate that after inhalation and oral exposure, bromomethane is absorbed and distributed throughout the body (Bond et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985). Bromomethane undergoes initial metabolism primarily by nucleophilic displacement of the bromide ion. When the attacking species is water, the products are methanol and bromide ion (Gargas and Andersen 1982; Honma et al. 1985). Bromomethane may also react with organic thiols (R-SH) to yield S-methyl derivatives (Iwasaki 1988b). No studies were located regarding excretion of bromomethane in humans after exposure. In animals exposed to bromomethane vapors, excretion occurs mainly by expiration of carbon dioxide or by urinary excretion of nonvolatile metabolites (Bond et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985). Only small amounts are excreted in the feces. Very little parent bromomethane is exhaled (Jaskot et al. 1988; Medinsky et al. 1985).

Bromomethane exists as a gas at ordinary temperatures, so the most likely route of human exposure is by inhalation. Only limited information is available on the effects of long-term inhalation exposure of humans to low levels of bromomethane. Headache, weakness, and increased prevalence of neurological signs such as muscle ache, fatigue, dizziness, and ataxia have been noted in workers exposed for extended periods in the workplace (Anger et al. 1986; Hine 1989; Kantarjian and

Shasheen 1963; Kishi et al. 1988). No cases of severe neurological effects from long-term exposure to low levels have been noted in humans. Acute inhalation exposure to bromomethane can result in marked lung irritation (edema, hemorrhagic lesions), and this may lead to moderate to severe impairment of respiratory function (Greenberg 1971; Prain and Smith 1952). Anuria and proteinuria are common signs of renal injury in acutely exposed humans (O'Neal 1987; Prain and Smith 1952; Viner 1945), but dose-response data are not available.

Acute inhalation exposure to bromomethane can result in marked lung irritation (edema, hemorrhagic lesions) (Irish et al. 1940; Kato et al. 1986; Reuzel et al. 1987; Sato et al. 1985). Mild signs of liver injury (edema, focal hemorrhages, minimal necrosis) have been noted in some studies at levels of 150-600 ppm (Alexeeff et al. 1985; Eustis et al. 1988; Hurtt et al. 1987a; Kato et al. 1986), with no significant injury at levels of 66 ppm (Irish et al. 1940). Signs of renal injury have been reported in several animal studies, including swelling, edema, nephrosis, and tubular necrosis (Alexeeff et al. 1985; Eustis et al. 1988). Inhalation studies in animals confirm that the central nervous system is injured by inhalation exposure to bromomethane. Clinical effects that have been detected include tremors, ataxia, paralysis, and seizures (Alexeeff et al. 1985; Anger et al. 1981; Breslin et al. 1990; Drew 1984; Haber 1987; Hurtt et al. 1987a; Irish et al. 1940; Kato et al. 1986). Histological lesions in the brain (focal necrosis and hemorrhage) have also been detected(Alexeeff et al. 1985; Eustis et al. 1988; Hurtt et al. 1987a).

Several studies of animals exposed to bromomethane vapors up to 70 ppm did not detect developmental effects, even though these concentration levels resulted in maternal toxicity (Hardin et al. 1981; Sikov et al. 1980). However, exposure of rabbits to 80 ppm during gestation resulted in increased incidence of several developmental anomalies in the off-spring (Breslin et al. 1990). These data suggest bromomethane may cause developmental effects, but only at high doses where other effects would also be of concern. Inhalation exposure of male rats to high levels of bromomethane (120-400 ppm) has resulted in decreased sperm production along with testicular degeneration and atrophy (Drew 1984; Eustis et al. 1988; Kato et al. 1986). However, exposures up to 70 ppm do not appear to interfere with reproductive functions in male (McGregor 1981) or female rats (Hardin et al. 1981; McGregor 1981; Sikov et al. 1980). Several studies in animals have shown that repeated (90-day) administration of concentrated solutions of bromomethane (40-5,000 mg/L, dissolved in oil) by gavage to rats can result in irritation and hyperplasia of the epithelium in the forestomach (Boorman et al. 1986; Danse et al. 1984).

The RfD for bromomethane is based on a 13-week subchronic oral study conducted in rats (Danse et al. 1984). The duration adjusted NOAEL of 1.4 mg/kg-day for gastric lesions was divided by an uncertainty factor of 1000 (10 to extrapolate from rats to humans; 10 to protect sensitive humans and 10 for extrapolating from subchronic to chronic exposure) to arrive at a chronic RfD for bromomethane of 1.4E-03 mg/kg-day (IRIS, 2003).

The RfC for bromomethane is based on a chronic inhalation conducted in rats (Reuzel et al., 1987, 1991). Degenerative and proliferative lesions of the olfactory epithelium of the nasal cavity were selected as the critical effect for derivation of the RfC. The duration adjusted LOAEL was used to calculate a human equivalent concentration (HEC) of 0.48 mg/m^3 which was divided by an

uncertainty factor of 100 (10 for intraspecies uncertainty, a factor of 3 for the use of a LOAEL for a mild effects and a factor of 3 for interspecies extrapolation because dosimetric adjustments have been applied. The factors of 3 represent operational application of a geometric half of the standard factor of 10, rounded to a single significant figure. As a result, multiplication of two factors of 3 results in a composite factor of 10) to arrive at a chronic RfC for bromomethane of 5E-03 mg/m^3 (IRIS, 2003).

Bromomethane has produced positive results in a number of mutagenicity test systems, both in vitro and in vivo. This effect does not appear to require metabolic activation, which is consistent with the fact the bromomethane is a direct-acting alkylating agent which can methylate DNA (Ikawa et al. 1986; Starratt and Bond 1988). This property suggests that bromomethane might be carcinogenic, but this has not been established.

No epidemiological studies were located on cancer incidence in humans exposed specifically to bromomethane. Chronic inhalation studies performed in mice and rats revealed no evidence of carcinogenic effects at exposure levels of 33-90 ppm (Reuzel et al. 1987; Yang 1990). Rats given daily oral doses of 50 mg/kg/day for 90 days developed inflammation and keratosis of the forestomach, along with lesions that were originally interpreted as squamous carcinomas (Danse et al. 1984). However, reevaluation of the histological specimens by NTP scientists indicated that the forestomach lesions in this study were hyperplastic but not neoplastic (ATSDR, 1992).

Bromomethane has been classified as a Group D carcinogen; not classifiable as to human carcinogenicity. This classification is based upon inadequate human and animal data: a single mortality study from which direct exposure associations could not be deduced and studies in several animal species with too few animals, too brief exposure or observation time for adequate power. Bromomethane has shown genotoxicity (IRIS, 2003).

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2-Butanone (MEK)

General Background

Physical/Chemical Properties

The chemical identify and physical/chemical properties of methyl ethyl ketone are summaried in Table 1.

Characteristic/Property	Data	Reference
CAS No.	78-93-3	
Common Synonyms	2-Butanone, MEK	Verschureren 1983
Molecular Formula	C4H80	
Chemical Structure	O	
	‖	
	CH3-C-CH2-CH3	
Physical State	Liquid	Budavari 1989
Molecular Weight	7.210	Budavari 1989
Melting Point	-86⌀C	Budavari 1989
Boiling Point	79.6⌀C	Budavari 1989
Water Solubility	353 g/L @ 10⌀C;	
	190 g/L @ 90⌀C	Verschueren 1983
Specific gravity	0.805 @ 20/4⌀C	Verschueren 1983
Vapor Density (air = 1)	2.41	Verschueren 1983
KOC	4.5 -50 (estimated	U.S. EPA 1989
Log KOW	0.29 (estimated)	U.S. EPA 1989
Vapor Pressure	77.5 mm Hg @ 20⌀C	Verschueren 1983
	98.0 mm Hg @ 25⌀C	U.S. EPA 1985
Henry's Law Constant	4.16 to 6.11 X 10-5	
	atm-3/mol	
	@25⌀C (estimated)	U.S. EPA 1985
Odor Threshold	5 to 10 ppm (in air)	U.S. Air Force 1989

There are three methyl ethyl ketone producers in the United States. In 1992, an estimated 494

million pounds of methyl ethyl ketone were produced in the US. During that same year, 55 million pounds were imported into the US and 112 million pounds were exported (Mannsville 1993). Methyl ethyl ketone is used in a number of industrial applications. The primary use of methyl ethyl ketone, accounting for approximately 63 percent of all use, is as a solvent in protective coatings. It is also used as a solvent in adhesives; printing inks; paint removers; in the production of magnetic tapes; and in dewaxing lubricating oil. Methyl ethyl ketone is used as a chemical intermediate in several reactions, including condensation; halogenation; ammonolysis; and oxidation. Small amounts of methyl ethyl ketone are also used as a sterilizer for surgical instruments, hypodermic needles, syringes and dental instruments; as an extraction solvent for hardwood pulping and vegetable oil; and as a solvent in pharmaceutical and cosmetic production (Mannsville 1993; HSDB 1994).

Environmental Fate and Transport

Of the total methyl ethyl ketone released to the environment almost all eventually enters the air. Methyl ethyl ketone is released into the environment from industrial and domestic uses. Methyl ethyl ketone has been found in cigarette smoke (500 ppm) and in gasoline engine exhaust (<0.1-1.0 ppm) (Verschueren 1983). Its use as a solvent in polyvinyl chloride pipe joint cement has introduced the chemical into drinking water (4.5 ppm, 6 months after installation) (HSDB 1994). It occurs naturally and has been found in a number of foods and beverages including swiss cheese (0.3 ppm), cream (0.154-0.177 ppm), barley, bread, honey, oranges, black tea, rum, non-alcoholic beverages (70 ppm), and ice cream (270 ppm) (HSDB 1994). Although the atmospheric concentration of methyl ethyl ketone increases during episodes of severe photochemical smog (up to 14 ppb in Los Angeles, CA during a photochemical pollution episode), ambient concentrations are usually below the detection limit (0.01 ppb) in most urban areas. Methyl ethyl ketone is not expected to be retarded by adsorption to soils rich in organic material [estimated Koc = 4.5-50 (U.S.EPA 1989)]; therefore, it is expected to be mobile in soil and, subject to leaching from landfills. The relatively high vapor pressure [98.0 mm Hg @ 25oC (U.S. EPA 1985)] and estimated Henry's Law constant (4.16-6.11 x 10-5 atm m3/mol @ 25oC) indicate that it can volatilize from moist and dry soil (HSDB 1994). It does not adsorb significantly to suspended solids, and will volatilize to the atmosphere from surface waters (HSDB 1994; U.S. EPA 1985). In wet or dry soil, methyl ethyl ketone will volatilize to air and may undergo photolysis on the soil surface (U.S. EPA 1985). It is also highly mobile and may be leached from the soil by water, and has been shown to be degradated by cultures of soil bacteria (U.S. EPA 1985). The most important fate process for methyl ethyl ketone in water is volatilization (estimated half-times of 3 and 12 days, for rivers and lakes, respectively). Complete aerobic biodegradation of methyl ethyl ketone has been reported in about 5-10 days following inoculation with sewage or polluted surface water. Longer times were required for degradation in marine water. Anaerobic degradation occurred after an acclimation period of about one week (HSDB 1994). Direct photolysis near the surface is also thought to be a possible mechanism, but was not measured (HSDB 1994). It is not expected to undergo chemical hydrolysis or to be bound to sediment or suspended organic matter (HSDB 1994). Methyl ethyl ketone is not expected to bioconcentrate in fish or aquatic organisms; its estimated fish bioconcentration factor is less than 1 (U.S. EPA 1985).

Absorption Transport and Degradation

Studies in humans and animals have demonstrated that methyl ethyl ketone can be absorbed via the lungs, the skin, and the gastrointestinal system. Pulmonary absorption values range from 41.1% to 55.8% (WHO 1993). The relative uptake through the lungs by humans was about 53% through a 4 hour exposure at 200 ppm (HSDB 1994: WHO 1993). Oral studies in rats have demonstrated that the peak blood level of methyl ethyl ketone (0.95 mg/mL) was reached in 4 hours following oral administration of the chemical in water (1690 mg/kg) (U.S. EPA 1985). Methyl ethyl ketone can also be absorbed through intact human skin. Absorption is more rapid through moist skin than through dry skin, and the rate of percutaneous absorption has been estimated to range from 5 to 10 micrograms/cm2/min (WHO 1993). The relative solubility of methyl ethyl ketone in various human tissues and organs compared to blood (tissue/blood partition coefficient) was shown to be similar in the kidney, liver, brain, heart, and lung and in fat and muscle tissue. This indicates a potential for even and widespread distribution of methyl ethyl ketone in human tissues (U.S. EPA 1985). It has also been shown to cross the placenta and enter the human fetus (WHO 1993). Experiments with guinea pigs and rats have shown that methyl ethyl ketone is metabolized by oxidative hydroxylation, forming 3-hydroxy-2-butanone, which is further reduced to 2,3-butanediol. Methyl ethyl ketone is also reversibly reduced to 2-butanol (U.S. EPA 1985). The half-life of methyl ethyl ketone in the blood of guinea pigs was reported to be 270 minutes, following intraperitoneal injection of 450 mg/kg. The clearance time was 12 hours (U.S. EPA 1985). It has been estimated that humans eliminate 30 to 40% of methyl ethyl ketone intake in expired air (HSDB 1994). The unchanged chemical and its metabolite, 3-hydroxy-2-butanone were measured in the urine of workers occupationally exposed to 8 to 272 mg/m3. The metabolite was only identified in workers exposed to the higher levels, and was correlated with the level of exposure and the urinary concentration of methyl ethyl ketone (U.S. EPA 1985). The plasma half-time in humans has be estimated at 49-96 minutes with an apparent clearance rate of 0.6 L/minute (ATSDR 1992).

Non-Carcinogenic Health Effects

Acute Toxicity

Humans - Volunteers complained of mild nose and throat irritation when exposed to 100 ppm. The irritation became objectionable when the concentration was raised to 300 ppm (ATSDR 1992). Workers occupationally exposure to an atmosphere containing 300 to 500 ppm (126 to 210 mg/kg/day) (see end note 2) complained of headaches, nausea, and respiratory tract irritation. Momentary exposure to 33,000 or 100,000 ppm caused intolerable irritation of the eyes, nose and throat (Krasavage et al. 1982). Workers exposed either by inhalation (300-600 ppm) or by skin contact to methyl ethyl ketone developed numbness in the extremities and dermatitis. High concentrations can result in central nervous system depression (see Section IV.G.1.). Eye contact with liquid methyl ethyl ketone causes painful irritation, and can result in comeal injury (Krasavage et al. 1982; HSDB 1994).

Animals - Oral LD50 values of 2737 and 4050 mg/kg were reported for rats and mice, respectively. Inhalation LC50 values of 23,500 mg/m3/8 hours for rats and 40,000 mg/m3/2 hours for mice were reported (U.S. EPA 1985). Guinea pigs exposed to 10,000 ppm methyl ethyl ketone developed liver and kidney congestion, but no effects were seen at 3500 ppm (ATSDR 1992).

Subchronic/Chronic Effects

Humans - Dermatitis, gastrointestinal upset, loss of appetite and weight, and neurological problems (see Section IV.G.I.) were reported by individuals occupationally exposed to methyl ethyl ketone, apparently in the absence of other solvents (WHO 1993). Neurological problems were also reported by workers chronically exposed to 300-600 ppm of the chemical (WHO 1993). All other available studies describing subchronic/chronic occupational exposure involved a mixture of organic solvents that contained methyl ethyl ketone. A variety of nervous system effects were consistently described after prolonged exposure to these mixtures (see Section IV.G.1.) (WHO 1993).

Animals - Male and female Fischer 344 rats were exposed to 0, 1250, 2500, or 5000 ppm methyl ethyl ketone by inhalation 6 hours/day, 5 days/week, for 90 days. No treatment related differences in food consumption, in eye effects, in neurological functioning, or in histopathologies were reported (U.S. EPA 1985). Increased serum alanine amino transferase in females was the only effect at 2500 ppm; increased absolute and relative liver weight were seen in both sexes at 5000 ppm. Females also developed decreased relative brain weight, and increased blood levels of alkaline phosphatase, glucose, and potassium at 5000 ppm. The mean body weights of both sexes were decreased at 5000 ppm, but increased at the other dose levels compared to the controls.

In another inhalation study Fischer 344 rats were exposed by inhalation to 5041 ppm (14,870 mg/m3), 2518 ppm, or 1254 ppm methyl ethyl ketone for 6 hours/ day, 5 days/week for 90 days. No significant effects on food consumption, eyes, or morphology were observed (WHO 1993). Increased absolute and relative liver weight, decreased body weight, increased relative kidney weight, decreased relative brain and spleen weights, and increased mean corpuscular hemoglobin were reported at the high dose. Increased body weights were reported at the low and intermediate dose.

Male rats exposed to 10,000 ppm methyl ethyl ketone 8 hours/day, 7 days/week developed severe irritation in the upper respiratory tract within a few days and died during the 7th week of exposure of bronchopneumonia (ATSDR 1992).

Carcinogenic Health Effects

Humans - No excess cancer incidence was found in an epidemiological study of 446 male workers in two methyl ethyl ketone dewaxing plants. The deaths observed were below the expected, and overall deaths from cancer were also below the expected. An increase in tumors of the buccal cavity and pharynx was seen but the numbers were small (2 observed, 0.13 expected) and lung cancers were significantly decreased (I observed, 6.02 expected) (ATSDR 1992; WHO 1993). The overall cancer-related mortality was less than expected in another epidemiological study of 1008 male oil refinery workers exposed to 1-4 ppm methyl ethyl ketone. There were no increases in buccal and pharyngeal cancers seen in this study (ATSDR 1992).

Animals - Methyl ethyl ketone was applied to the skin of mice twice weekly for one year (50 mg/dose). No tumors were reported (U.S. EPA 1989). No information on the carcinogenicity of

methyl ethyl ketone by other routes of administration were found in the secondary sources searched.

Mutagenicitv

Results from four out of the five short term mutagenicity assays, requested by and submitted to EPA under the Toxic Substances Control Act (TSCA), indicate methyl ethyl ketone is not mutagenic. Methyl ethyl ketone is negative in the Ames test (in Salmonella typhimurium strains TA98, TA 100, TA 1535, and TA 1537 with or without S-9 metabolic activation); the mouse lymphoma test; the cell transformation assay; and the mouse micronucleus test. Results from the Section 4 unscheduled DNA test was concluded to be positive (Cimino 1985).

Most of the information from other secondary sources also indicate that methyl ethyl ketone is not genotoxic. Methyl ethyl ketone was negative in E. coli tester strains WP2 and WP2uvrA (WHO 1993). It was negative in the mitotic gene conversion assay in S. cerevisiae tester strain JD 1 (WHO 1993). It was negative in the micronucleus test in both CD I mice and Chinese hamsters (WHO 1993). It was a strong inducer of aneuploidy in S. cerevisiae strain D6 LM (U.S. EPA 1989).

Developmental/Reproductive Toxicity

Animal studies indicate that exposure to high methyl ethyl ketone concentrations in air breathed during pregnancy can cause fetal toxicity and possibly adverse developmental effects. EPA has derived an oral reference dose (RfD) (see end note 3) of 0.6 mg/kg/day, based on developmental effects of a metabolite (2-butanol) of MEK. EPA has derived an inhalation reference concentration (RfC) (see end note 4) of 1 mg/m') for methyl ethyl ketone, based on its developmental effects.

Humans - No information on the developmental/reproductive toxicity of methyl ethyl ketone was found in the secondary sources searched.

Animals - Since there are no appropriate oral studies on methyl ethyl ketone, the U.S. EPA (1994) calculated a chronic oral RfD for methyl ethyl ketone of 0.6 mg/kg/day, based on decreased birth weights seen in a multigeneration study with its metabolic intermediate, 2-butanol. Male and female Wistar rats (30/sex/group) were given 2-butanol in drinking water at 0, 0.3, 1.0, or 3.0% nine weeks before mating through gestation and lactation. The high dose was reduced to 2.0°/a for the second generation. Decreased fetal weight and decreased pup survivability were reported for the first generation at 3.0% 2-butanol. Decreased fetal weight was seen in the second generation at 2.0%. Increases in the incidences of missing stemebrae, wavy ribs, and incomplete vertebrae ossification at 2%, compared to the 1.0 and 0.3% groups, were seen. However, because of high incidences of these developmental effects in the control group, they could not be determined to be treatment related. The 1.0% dose, equivalent to 1771 mg/kg/day, was identified as a no-adverse-effect-level (NOAEL), and the 2.0% dose was identified as a lowest-adverse-effect-level (LOAEL)(U.S. EPA 1994).

The U.S. EPA (1994) calculated a chronic inhalation reference concentration (RfC) of 1.0 mg/m3 for methyl ethyl ketone, based on decreased fetal birth weight seen in a mouse inhalation study. Pregnant mice were exposed by inhalation to atmospheric concentrations of 0, 398, 1010, or 3020

ppm methyl ethyl ketone 7 hours/day during days 6-15 of gestation. Decreased fetal body weight was seen at 3020 ppm. There was an increased incidence of fetuses and litters with malformations in the treated groups, but the increases were not statistically significant. A NOAEL of 1010 ppm and a LOAEL of 3020 ppm were identified (U.S. EPA 1994).

Groups of 25 pregnant Sprague-Dawley rats were exposed to air concentrations of 400, 1000, or 3000 ppm methyl ethyl ketone 7 hours/day during days 6-15 of gestation. The control group contained 35 rats. Maternal body weight gain was decreased and water consumption was increased in dams receiving 3000 ppm. There were no treatment related effects on the pregnancy rate, the number of implantations per litter, or the percent live fetuses. A total of five fetuses with at least one external or soft tissue malformation were reported, but were distributed in all groups including the control. Increased incidences of delayed ossification and extra ribs at the 3000 ppm dose were attributed to fetal toxicity (U.S. EPA 1989).

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Carbon Disulfide

Carbon disulfide is a colorless liquid with a pleasant, sweet odor. If impure, it takes on a yellowish

color and an unpleasant odor. It evaporates at room temperature. The vapor is twice as heavy as air. It is flammable and explosive. Commercial carbon disulfide is made by combining carbon and sulfur at high temperatures. It is used to make rayon, cellophane, and carbon tetrachloride. In smaller amounts, it is used to dissolve rubber and in the manufacture of some pesticides.

Carbon disulfide evaporates rapidly when released to the environment (half-life of 1 to 10 weeks). Most carbon disulfide is air and surface water is from manufacturing and processing activities. Once released to the air, it will break down into simpler components after approximately 12 days. If released to soil, it moves through the soil relatively quickly (i.e., it does not bind to soil) into groundwater. Once dissolved in water, it is relatively stable.

Humans may be exposed to carbon disulfide in the air that is breather, and in the food and water that is ingested. Exposure by skin contact may also occur. By all three routes of exposure, carbon disulfide rapidly enters the bloodstream and widely distributes throughout the body. A small amount of carbon disulfide will exit the body in an unchanged form via the lungs. Most is biotransformed with breakdown products eliminated from the body via urine.

At high levels of exposure, carbon disulfide may cause life-threatening effects on the nervous system and heart. Lesser exposures result in headaches, tiredness, and difficulty sleeping. Long-term exposures may also result in liver damage. Pregnant animals, after exposure, had miscarriages or offspring with birth defects. Skin contact can result in chemical burns and blistering. No information is available on the potential of carbon disulfide to produce cancer in humans or laboratory animals.

Agency for Toxic Substances and Disease Registry (ATSDR). 2002. *Toxicological Profile for Carbon Disulfide*. U.S. Department of Health and Human Services. Public Health Service.

Chlorobenzene

Chlorobenzene occurs as a colorless flammable liquid, with low solubility in water. The primary uses of chlorobenzene are as a solvent for pesticide formulations, diisocyanate manufacture, and degreasing automobile parts and for the production of nitrochlorobenzene. In the past, chlorobenzene was used as an intermediate in phenol and DDT production (ATSDR, 1997).

Chlorobenzene is readily absorbed via inhalation and oral exposure. After inhalation exposure Chlorobenzene appears to preferentially distribute to adipose tissue due to its lipophilic nature. Chlorobenzene is primarily excreted as a mercapturic acid conjugate in the urine (ATSDR, 1990). Human exposure to chlorobenzene appears to be primarily occupational. In urban areas, chlorobenzene may be released to the ambient air during its manufacture and use. Chlorobenzene or its breakdown products can be detected in urine, exhaled breath, blood, and body fat to determine whether or not exposure has occurred. A child who ingested chlorobenzene became unconscious and cyanotic and had muscle spasms but recovered completely (ATSDR, 1997). Acute (short-term) inhalation exposure of cats to chlorobenzene produced narcosis, restlessness, tremors, and muscle spasms (HSDB, 2003). Acute animal tests, such as the LC_{50} and LD_{50} tests in rats, mice, rabbits,

and guinea pigs, have demonstrated chlorobenzene to have low acute toxicity by inhalation and moderate acute toxicity from oral exposure (RTECS, 1993).

Chronic (long-term) exposure of humans to chlorobenzene affects the CNS. Signs of neurotoxicity include numbness, cyanosis, hyperesthesia (increased sensation), and muscle spasms. Headaches and irritation of the mucosa of the upper respiratory tract and eyes have also been reported in humans chronically exposed via inhalation (USEPA, 1989). No studies were located demonstrating that chlorobenzene causes hepatic toxicity in humans by any route of exposure (ATSDR, 1990). The CNS, liver, and kidneys have been affected in animals chronically exposed to chlorobenzene by inhalation (ATSDR, 1997). Chronic ingestion of chlorobenzene has resulted in damage to the kidneys and liver in animals (USEPA, 1989).

No studies were found regarding the developmental and reproductive toxicity of chlorobenzene in humans. In inhalation and oral exposure studies, the animals did not demonstrate significant developmental toxicity when compared with untreated controls. Negative responses in two animal species suggest that developmental toxicity may not be an area of concern for chlorobenzene. In a two-generation inhalation study, chlorobenzene did not adversely affect various reproductive parameters in rats (Nair et al. 1987).

The RfD for chlorobenzene is based on a 13-week subchronic oral study conducted in dogs (Monsanto, 1967; Knapp, et al., 1971). The duration adjusted NOAEL of 19 mg/kg-day for histopathologic changes in the liver was divided by an uncertainty factor of 1000 (10 to extrapolate from rats to humans; 10 to protect sensitive humans and 10 for extrapolating from subchronic to chronic exposure) to arrive at a chronic RfD for Chlorobenzene of 2E-02 mg/kg-day (IRIS, 2003).

The NCEA Superfund Technical Support Center has derived a provisional RfC for Chlorobenzene. The provisional RfC is based on a two-generation reproductive study in rats (Nair et al, 1987). Liver enlargement with associated centrilobular hepatocellular hypertrophy was selected as the critical effect for derivation of the RfC. The duration adjusted NOAEL was used to calculate a human equivalent concentration (HEC) of 58 mg/m^3 was divided by an uncertainty factor of 1000 (3 extrapolate from rats to humans using dosimetric adjustments; 10 to protect sensitive humans; 10 to extrapolate from a subchronic to a chronic study; and 3 for database deficiencies) to arrive at a chronic RfC for chlorobenzene of 6E-2 mg/m^3 (NCEA, 1998).

No studies were located regarding the genotoxic effects of chlorobenzene in humans. No in vivo animal assays were found, except the micronuclear test in mice, which was moderately positive (Mohtashamipur et al. 1987). Furthermore, in vitro tests employing bacterial and yeast assay systems with and without metabolic activation were negative (Haworth et al. 1983; NTP 1985; Prasad 1970).

No studies were found regarding the carcinogenicity of chlorobenzene in humans. In a chronic bioassay in animals, chlorobenzene (up to 120 mg/kg/day) did not produce increased tumor incidences in mice of both sexes or in female rats (NTP 1985). It was noted, however, that male rats showed a statistically significant increase in neoplastic nodules at the highest dose level tested. While there is strong evidence for neoplastic nodules, existing data are inadequate to characterize

the potential for chlorobenzene to cause cancer in humans and animals (ATSDR, 1990).

The USEPA has classified Chlorobenzene as a Group D carcinogen; not classifiable as to human carcinogenicity. The basis for this classification is a lack of human data, inadequate animal data and predominantly negative genetic toxicity data in bacterial, yeast, and mouse lymphoma cells (IRIS, 2003).

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Chlorodibromomethane

Chlorodibromomethane is colorless, heavy, nonburnable liquid with the sweetish odor. It was used in the past to make other chemicals, such as fire extinguisher fluids, spray can propellants, refrigerator fluid, and pesticides. Currently, it is produced only in small compounds for use in laboratories. Another source of chlorodibromomethane is drinking water. When chlorine is added to tricky water to kill any disease-causing organisms, which might be present, the chlorine reacts with natural substances found in the water, reducing low levels of chlorodibromomethane as an undesired byproduct. Small amounts are also produced by plants in the ocean (ATSDR, 1990).

There is limited information regarding chlorodibromomethane absorption in humans or animals following exposure. Based on the physical-chemical properties of this compound, and by an analogy with other related halomethanes, such as chloroform, it is expected that chlorodibromomethane would be across the lung and skin. Mink et al. (1986) found that 60% to 90% of single oral doses of this compound given in corn oil to rats or mice were recovered in expired air, urine, or in internal organs. This indicates that gastrointestinal absorption was at least 60% to 90% complete. This is consistent with the ready gastrointestinal absorption observed for other halomethanes, such as chloroform or carbon tetrachloride (ATSDR, 1990). There is limited information regarding the distribution of chlorodibromomethane after exposure. Data seems to indicate that after oral exposure, chlorodibromomethane is absorbed from the stomach and distributed throughout the body (Roth, 1904, as cited in von Oettingen 1955, Mink et al., 1986). The first step in the metabolism of chlorodibromomethane is oxidation by the cytochrome P-450 mixed function oxidase system of liver to a dihalocarbonyl molecule. This dihalocarbonyl molecule (an analogue of phosgene) is highly reactive, and may undergo a number of reactions, including: (a) direct reaction with cellular nucleophiles to yield covalent adducts; (b) reaction with two moles of glutathione (GSH) to yield carbon monoxide and oxidized glutathione (GSSG): and (c) hydrolysis to yield CO_2 (ATSDR, 1990). Excretion primarily occurs via excretion of the parent compound or of CO_2.

The chief systemic effects recognized following exposure to chlorodibromomethane is injury to the liver and the kidneys. These effects have been investigated mostly in animals exposed by the oral route, but there is limited data indicating that similar effects occur following inhalation exposure as well. Typical effects in liver include increased liver weight, vacuolization, and fat accumulation (Condie et al., 1983, NTP, 1985, Tobe et al., 1982, Munson et al., 1982). Effects in kidney are

usually characterized by tubular degeneration and mineralization, leading to nephrosis and decreased renal function (Condie et al. 1983: NTP 1985). Oral dose levels leading to renal and hepatic effects in animals vary somewhat between species and sexes. Other systemic effects of chlorodibromomethane appear to be minor or absent. Exposure to chlorodibromomethane, like other volatile halogenated hydrocarbons, can lead to marked central nervous system depression.

The developmental effects of oral exposure to chlorodibromomethane have not been extensively investigated, but limited data suggest this chemical has relatively low toxicity on the developing fetus (Ruddick et al., 1983). Chronic exposure of rats and mice to chlorodibromomethane (80 to 100 mg/kg/day) resulted in no detectable histological effects in reproductive tissues of males (testes, prostate, and seminal vesicles) or females (ovaries, uterus, and mammary gland) (NTP, 1985).

The RfD for chlorodibromomethane is based on a 13-week subchronic oral study conducted in rats (NTP, 1985). The duration adjusted NOAEL of 21.4 mg/kg-day for hepatic lesions was divided by an uncertainty factor of 1000 (10 to extrapolate from rats to humans; 10 to protect sensitive humans and 10 for extrapolating from subchronic to chronic exposure) to arrive at a chronic RfD for chlorodibromomethane of 2E-02 mg/kg-day (IRIS, 2003).

Neither IRIS (2003) nor HEAST (1997) carry a verified RfC for chlorodibromomethane.

The genotoxicity of chlorodibromomethane has been investigated in a number of studies, both in vitro and in vivo. The results of the studies are generally mixed and are occasionally inconsistent, perhaps because of variations in the efficiency of extrinsic or intrinsic metabolic activation of the parent compounds under test conditions. Still, a number of studies found evidence for both mutagenic and cytogenic effects by chlorodibromomethane (ATSDR, 1990).

No studies are located regarding carcinogenic effects in humans following oral exposure to chlorodibromomethane. Chronic oral studies in animals indicate that chlorodibromomethane has carcinogenic effects. Chronic exposure to chlorodibromomethane resulted in an increased incidence of liver tumors (adenomas or carcinomas) in mice (but not in rats) (NTP, 1985).

The EPA has classified chlorodibromomethane as a Group C compound, possible human carcinogen, based on adequate human data and limited evidence of carcinogenicity in animals; namely, positive carcinogenic evidence in B6C3F1 mice (males and females), together with positive mutagenicity data, and structural similarity to other trihalomethanes, which are known animal carcinogens (IRIS, 2003). The oral slope factor for this compound is 8.4E-02 $(mg/kg\text{-}d)^{-1}$ and is based upon hepatocellular adenoma or carcinomas in female mice in a two-year carcinogenicity bioassay (NTP, 1985). There is no inhalation unit risk value available for this compound.

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Chloroethane

Chloroethane, also called ethyl chloride, is a colorless gas at room temperature and pressure. In pressurized containers, chloroethane exists as a liquid. However, the liquid evaporates quickly when exposed to air. It catches fire easily and is very dangerous when exposed to heat or flame. Chloroethane does not occur naturally in the environment. It is present in the environment as a result of human activity. In the past, the largest single use for chloroethane was for the production of tetraethyl lead, which is a gasoline additive. However, production of chloroethane has decreased dramatically as a result of stricter government regulations controlling lead in gasoline. Other

applications include use in the production of ethyl cellulose, dyes, medicinal drugs, and other commercial chemicals, and use as a solvent and refrigerant. It is used to numb skin prior to medical procedures such as ear piercing and skin biopsies, and it is used in the treatment of sports injuries (ATSDR, 1998).

Chloroethane is readily absorbed through the lungs in humans and animals (Konietzko 1984; Lehman and Flury 1943; Torkelson and Rowe 1981). No studies were located regarding absorption in humans or animals following oral exposure to chloroethane. A dermal flux rate of 0.99 mg/cm2/hour was estimated based on the physical properties of chloroethane (Fiserova-Bergerova et al. 1990). Based on physical properties, the study authors considered chloroethane to have no significant dermal absorption potential. No quantitative studies were located regarding absorption in humans or animals following dermal exposure to chloroethane (ATSDR, 1998). Chloroethane has a higher affinity for fat than for blood, liver, or muscle (Gargas et al. 1989). It is unknown if chloroethane can reach and cross the placenta or its precursors. However, based on physical-chemical characteristics of the compound, it is likely that it can. In addition, it is known that some chloroethane metabolites such as ethanol (Guzelian et al. 1992) can cross the placental barrier. One study to date (Pellizari et al. 1982) determined that chloroethane does enter the milk of a lactating woman and can be detected. However, this study did not quantify the chloroethane in milk, few women were tested, and the route of exposure to chloroethane was not determined. No studies were located regarding metabolism of chloroethane by humans. A review indicates that a small amount of chloroethane was metabolized to ethanol via dechlorination in animals following administration of high anesthetic doses (Konietzko 1984). The species was not identified. The two major proposed pathways in rats and mice are the production of acetaldehyde by cytochrome 450, and conjugation of chloroethane with glutathione to form S-ethyl-glutathione (Fedtke et al. 1994b).

Since chloroethane primarily exists as a gas, inhalation is the primary route of exposure. Although chloroethane has been used as an anesthetic agent in humans, there is little data pertaining to the effects of chloroethane at low concentrations. Animal studies regarding the effects of chloroethane are predominantly focused on the inhalation route of exposure. At high concentrations for short periods of time, chloroethane clearly results in neurological effects producing unsteadiness followed by unconsciousness. A number of toxicity studies have not clearly identified a target organ of toxicity for chloroethane (Landry et al. 1982, 1987,1989; NTP 1989). One target of chloroethane toxicity in animals exposed to high concentrations is the uterus. Chloroethane has been shown to decrease uterine weight by 35% in mice exposed to 15000 ppm chloroethane, 6 hours/day for 5 days (Fedtke et al. 1994a). Significant decreases in uterine glutathione levels were also observed in both rats and r-nice (Fedtke et al. 1994b). Chloroethane has also been shown to produce uterine cancer in mice but not rats exposed to 15,000 ppm chloroethane for approximately 2 years (NTP 1989).

In addition to uterine effects, limited studies of reproduction and development in mice have shown effects. A small increase in the average duration of the estrous cycle was observed in mice exposed to 15,000 ppm chloroethane 6 hours/day for 21 days (Bucher et al. 1995). Evidence of fetotoxicity, a statistically significant increase in small centers of unossified bones of the skull, was observed in the offspring of mice exposed to 4,946 ppm chloroethane during gestation days 6-15 (Scortichini et al. 1986). Further studies are needed to confirm the reproductive and developmental toxicity of

chloroethane and to determine that the effects are observed in another species in addition to mice.

Neither IRIS nor HEAST carry a verified toxicity values such as an RfD for chloroethane. The NCEA has developed a provisional RfD for chloroethane of 4E-01 mg/kg/day as cited in the Region IX PRG Tables (USEPA, 2002).

The RfC for chloroethane is based on delayed fetal ossification in a mouse developmental inhalation study (Scortichini et al., 1986). The duration adjusted NOAEL was used to calculate a human equivalent concentration (HEC) of 4000 mg/m^3 which was divided by an uncertainty factor of 100 (a factor of 10 is used to account for sensitive populations. An uncertainty factor of 3 (rather than 10) is used for interspecies extrapolation due to dosimetric adjustment of the inhaled concentration. As no multigeneration reproductive study and no definitive developmental toxicity studies were available, a full factor of 10 is proposed for data base deficiencies) to arrive at a chronic RfC for chloroethane of 1E+1 mg/m^3 (USEPA, 2003).

Chloroethane is an alkylating agent and is mutagenic to Salmonella (NTP 1989). Chloroethane has not been shown to cause genotoxic effects in *in vivo* assays in mice (Ebert et al. 1994).

In a single high concentration (15,000 ppm) study, chloroethane clearly caused uterine cancer in female mice, with equivocal evidence of carcinogenicity in rats (increased skin tumors in male rats and astrocytomas in the brains of female rats) (NTP 1989). Because only one concentration was tested, it cannot be determined whether or not the carcinogenic effect of chloroethane is a high-concentration phenomenon.

A carcinogenicity assessment for lifetime exposure is not available at this time (IRIS, 2003; HEAST, 1997). The NCEA has developed a provisional oral and inhalation slope factor for chloroethane of 2.9E-03 $(mg/kg/day)^{-1}$ as cited in the Region IX PRG Tables (USEPA, 2002).

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Chloroform

Chloroform is a colorless, volatile liquid that is widely used as a general solvent and as an intermediate in the production of refrigerants, plastics, and pharmaceuticals (Torkelson and Rowe, 1976; IARC, 1976). Chloroform is rapidly absorbed from the lungs and the gastrointestinal tract, and to some extent through the skin. It is extensively metabolized in the body, with carbon dioxide as the major end product. The primary sites of metabolism are the liver and kidneys. Excretion of chloroform occurs primarily via the lungs, either as unchanged chloroform or as carbon dioxide (ATSDR, 1997).

Target organs for chloroform toxicity are the liver, kidneys, and central nervous system. Liver effects (hepatomegaly, fatty liver, and hepatitis) were observed in individuals occupationally exposed to chloroform (Bomski et al., 1967). Several subchronic and chronic studies by the oral or inhalation routes of exposure documented hepatotoxic effects in rats, mice, and dogs (Palmer et al., 1979; Munson et al., 1979; Heywood et al., 1979). Renal effects were reported in rats and mice following oral and inhalation exposures (Roe et al., 1979; Reuber, 1976; Torkelson et al., 1976), but evidence for chloroform-induced renal toxicity in humans is sparse. Chloroform is a central nervous system depressant, inducing narcosis and anesthesia at high concentrations. Lower concentrations may cause irritability, lassitude, depression, gastrointestinal symptoms, and frequent and burning urination (ATSDR, 1997).

Developmental toxicity studies with rodents indicate that inhaled and orally administered chloroform is toxic to dams and fetuses. Possible teratogenic effects were reported in rats and mice exposed to chloroform by inhalation (Schwetz et al.; 1974; Murray et al., 1979). Chloroform may cause sperm abnormalities in mice and gonadal atrophy in rats (Palmer et al, 1979; Reuber, 1979; Land et al., 1981).

A Reference Dose (RfD) of 0.01 mg/kg/day for subchronic and chronic oral exposure was calculated from a lowest-observed-adverse-effect level (LOAEL) of 15 mg/kg/day based on fatty cyst formation in the liver of dogs exposed to chloroform for 7.5 years (Heywood et al., 1979).

Epidemiological studies indicate a possible relationship between exposure to chloroform present in chlorinated drinking water and cancer of the bladder, large intestine, and rectum. Chloroform is one of several contaminants present in drinking water, but it has not been identified as the sole or primary cause of the excess cancer rate (ATSDR, 1997; U.S. EPA, 1985). In animal carcinogenicity studies, positive results included increased incidences of renal epithelial tumors in male rats, hepatocellular carcinomas in male and female mice, and kidney tumors in male mice (Jorgensen et

al., 1985; Roe et al., 1979; NCI, 1976).

Based on U.S. EPA guidelines, chloroform was assigned to weight-of-evidence Group B2, probable human carcinogen, on the basis of an increased incidence of several tumor types in rats and in three strains of mice. The carcinogen slope factor (q_1^*) for chloroform is 6.1E-3 $(mg/kg/day)^{-1}$ for oral exposure and 8.1E-2 $(\mu g/m^3)^{-1}$ for inhalation exposure. An inhalation unit risk of 2.3E-5 $(\mu g/m^3)^{-1}$ is based on hepatocellular carcinomas in mice in an oral gavage study.

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Chloromethane

Chloromethane, also known as methyl chloride, is a clear, colorless gas. It has a faint, sweet odor that is noticeable only at toxic levels. It is heavier than air and extremely flammable. Chloromethane is produced in industry, but it also occurs naturally with up to 99% of it released to the environment emanating from natural sources. Natural sources include chemical reactions occurring in the oceans or the burning of grass, wood, charcoal and coal.

In the past, chloromethane was widely used as a refrigerant, foam-blowing agent and as a pesticide or fumigant. Today, nearly all commercially produced chloromethane is used to make silicones, agricultural chemicals, methyl cellulose, quaternary amines and butyl rubber. It is also found as a pollutant in municipal waste streams and industrial waste streams as a result of formation or incomplete removal.

Most releases of chloromethane will be to the air. It breaks down very slowly (months to years) in the air. Chloromethane can dissolve in water, and small amounts may be found in surface water. Because chloromethane is a gas at room temperature, it evaporates quickly from water. Small amounts may move below the surface to groundwater where it breaks down slowly (months to years) unless acted upon by certain bacteria. Chloromethane does not concentrate in sediments, or in animals and fish in the food chain.

Chloromethane may enter the body by inhalation or ingestion. It rapidly enters the blood stream by both pathways, and distributes throughout the body. Most chloromethane is chemically changed in the body. It's breakdown products are eliminated by exhalation. A small amount of the breakdown products are eliminated in urine within a few days of exposure. Because chloromethane is a gas at room temperature, dermal contact is unlikely.

Brief exposures to high levels of chloromethane can cause convulsions, coma, and death. Low exposure levels result in blurred or double vision, dizziness, fatigue, personality changes, confusion, tremors, uncoordinated movements, nausea and vomiting. Symptoms can last for several months or years. Chloromethane can also cause liver and kidney damage, and can affect heart rate and blood pressure. Young animals exposed to chloromethane exhibited slow growth and brain damage. Male animals may have reduced fertility or sterility. Pregnant females lost their developing young upon exposure. It is not known whether chloromethane can cause sterility, miscarriages, birth defects or cancer in humans.

Male mice, after inhalation exposure to chloromethane for 2 years, developed kidney tumors. This effect was not noted in female mice or male/female rats. The EPA has classified chloromethane into Group C, possible carcinogen.

Agency for Toxic Substances and Disease Registry (ATSDR). 2002. *Toxicological Profile for Chloromethane*. U.S. Department of Health and Human Services. Public Health Service.

1,2-Dibromo-3-chloropropane

1,2-Dibromo-3-chloropropane is a colorless liquid with a sharp smell. It evaporates about as fast as water does, which is not very quickly. 1,2-Dibromo-3-chloropropane will dissolve in water to a very limited extent. It is a man-made chemical not found naturally in the environment. Some industries use 1,2-dibromo-3-chloropropane to make a chemical that is used to make materials resistant to burning. Large amounts of 1,2-dibromo-3-chloropropane were used in the past on certain farms to kill pests that were harmful to the crops. Farmers in Hawaii stopped using this chemical in 1985; use in other states stopped in 1979 (ATSDR, 1992).

No studies were located regarding the absorption and distribution of 1,2-dibromo-3-chloropropane by inhalation or dermal exposure in humans or animals. No studies were located regarding the absorption and distribution of 1,2-dibromo-3-chloropropane by humans after oral exposure. Animal studies show that 1,2-dibromo-3-chloropropane extensively absorbed from the gastrointestinal tract (Gingell, et al., 1987a, Kato, et al., 1979). In rats administered 14C-1,2-dibromo-3-chloropropane in corn oil by oral exposure, unchanged 1,2-dibromo-3-chloropropane accumulated only in the adipose tissues, while the unextractable metabolites were found in kidneys and livers (Kato et al. 1979). The unextractable metabolites were detected in most tissues, possibly as reactive metabolites bound to tissue macromolecules. The highest level of radioactivity was found in livers and kidneys (Kato et al. 1980) 6 and 20 hours postexposure. The metabolism of 1,2-dibromo-3-chloropropane was studied in rats. 1,2-dibromo-3-chloropropane is converted to epoxy derivatives, which are further hydrolyzed and debrominated. Bromide accumulates in the kidneys. Beside other metabolites, epichlorohydrin and epibromohydrin were found, which can be further metabolized to oxalic acid. Mercapturic acids were detected in urine and this indicates that metabolic intermediates reacted with nonprotein sulfhydryl (NPS) groups (Jones et al. 1979).

Epidemiological studies have indicated that the testes are the main target organ of 1,2-dibromo-3-

chloropropane toxicity following occupational exposures. Decreased spermatogenesis, atrophy of the seminiferous epithelium with azoospermia, and possible sex ratio differences in offspring were observed in exposed workers (Biava, et al., 1978, Potashnik, et al., 1978). Studies indicate that the testicular damage can be permanent (Egnatz, et al., 1980, Lantz, et al., 1981). Other effects reported by exposed workers include headache, nausea, lightheadedness, and weakness. No reproductive or carcinogenic effects were detected in a population exposed to concentrations of 1,2-dibromo-3-chloropropane ranging from 0.004 ppb to 5.75 ppb in drinking water (Wong et al. 1988, 1989).

In animals, effects after inhalation and oral exposures include mortality, fetotoxicity, hepatic (Torkelson, et al., 1961, Rao, et al., 1982, 1983, NTP, 1982) and renal lesions (Torkelson, et al., 1961, Saegusa, et al., 1982, NTP, 1982), gonadal atrophy (Torkelson, et al., 1961, Saegusa, et al., 1982, NTP, 1982), and cancer (NTP, 1982). Respiratory lesions and carcinomas of the respiratory tract were observed after inhalation exposure (Torkelson, et al, 1961, NTP, 1982), while gastrointestinal lesions and stomach carcinomas (Ghanayem, et al., 1986, NCI, 1978) were seen after oral exposure. In addition, anemia (Torkelson et al., 1961), central nervous system depression, and brain lesions were observed in animals after inhalation exposures (Torkelson, et al., 1961, Rao, et al, 1983, NTP, 1982).

Neither IRIS nor HEAST carry a verified toxicity values such as an RfD for 1,2-dibromo-3-chloropropane.

The RfC for 1,2-dibromo-3-chloropropane is based on testicular effects in a subchronic reproductive study in rabbits (Rao, et al., 1982). The duration adjusted NOAEL was used to calculate a human equivalent concentration (HEC) of 0.17 mg/m^3 which was divided by an uncertainty factor of 1000 (an uncertainty factor of 10 is used for the protection of sensitive human subpopulations. A factor of 3 is used for interspecies extrapolation, as the concentration was dosimetrically adjusted to humans. A full factor of 10 is applied for the use of a subchronic study to reflect the marginal NOAEL in the principal study, as the minor testicular effects seen at the NOAEL were consistent with the effects seen at the higher LOAEL in this and other investigations. A study of chronic duration could result in these minor effects progressing into more delineated adverse effects. A factor of 3 is used for data base deficiency because of the lack of a multigenerational reproductive study, and inhalation development toxicity studies) to arrive at a chronic RfC for 1,2-dibromo-3-chloropropane of 2E-04 mg/m^3 (IRIS, 2003).

Positive results were found in the reverse mutation assay in Salmonella typhimurium TA1535, TAlOO, and TA98 with metabolic activation but not without activation (Ratpan and Plauman 1988; Stolzenberg and Hine 1979). Purified 1,2-dibromo-3-chloropropane was considered a potent indirect mutagen. The mutagenic potential of 1,2-dibromo-3-chloropropane was demonstrated in humans by the evidence of a change in sex ratio among the offspring of exposed workers (Potashnik et al. 1984). Increased dominant lethality was reported in rats after inhalation (Rao 1983) and oral exposures to 1,2-dibromo-3-chloropropane (Teramoto et al. 1980). In contrast, no dominant lethal effect was observed in mice treated either orally for 5 days (Teramoto et al. 1980) or intraperitoneally or subcutaneously with a single injection of 1,2-dibromo-3-chloropropane

(Generoso et al. 1985). Positive results were obtained in mice in the spot test (Sasaki et al. 1986) but not in the specific locus gene mutation test (Russell et al. 1986).

Information regarding carcinogenicity of 1,2-dibromo-3-chloropropane in humans is sparse. Only two epidemiological studies regarding cancer risk were located. One did not report any increased incidence of cancer among exposed workers (Hearn et al. 1984). The other study found no correlation between the risk of gastric cancer in a population residing in an area where drinking water chloropropane (Wong et al. 1989). There is conclusive evidence of the carcinogenicity of 1,2-dibromo-3-chloropropane in experimental animals. Rats that were exposed to 1,2-dibromo-3-chloropropane by inhalation for 84-103 weeks developed multiple site neoplasms (NTP 1982). Adenomas and carcinomas of the respiratory tract and tongue in both sexes, fibroadenomas of the mammary gland and adenomas of the adrenal cortex in females, and trichoadenomas of the skin and mesotheliomas of the tunica vaginalis in males were observed in the exposed animals. In contrast, the development of neoplasms was restricted only to the respiratory tract in mice exposed to the same concentrations for 76-103 weeks (NTP 1982). When administered chronically by gavage, 1,2-dibromo-3-chloropropane induced squamous cell carcinomas of the forestomach in rats and mice of both sexes and carcinomas of the mammary gland in female rats (NCI 1978).

A carcinogenicity assessment for lifetime exposure is not available at this time on IRIS. An oral slope factor is available in HEAST (HEAST, 1997) and has been derived based upon a 104 week feeding study in rats (Hazleton Laboratories, 1977). HEAST has classified 1,2-dibromo-3-chloropropane as a B2 carcinogen and has developed an oral slope factor of 1.4E+0 $(mg/kg\text{-}d)^{-1}$. HEAST has developed an inhalation slope factor of 2.4E-03 $(mg/kg\text{-}d)^{-1}$ based upon an inhalation carcinogenesis bioassay conducted in rats and mice (NTP, 1982).

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Dichlorobenzenes

1,4-Dichlorobenzene, also referred to as para-DCB, p-DCB, paracide, Paramoth®, Parazene®, PDB, and Santochlor®, has a benzene ring with two chlorine atoms attached at the 1 and 4 carbon atoms; it does not occur naturally (ATSDR, 1997). Two additional isomers, 1,3-dichlorobenzene and 1,2-dichlorobenzene, also exist. 1,4-Dichlorobenzene is used to make mothballs, deodorant blocks used in restrooms, and in animal holding facilities to control odors (ATSDR, 1997). It also has applications in fumigants, insecticides, lacquers, paints, and seed disinfection products (Leber and Benya, 1994). Of the 1300 sites on the United States Environmental Protection Agency's National Priorities List, dichlorobenzenes have been identified on at least 244 sites. Drinking water samples from U.S. surface water sources, environmental hazardous waste sites, and food have been reported to contain dichlorobenzenes (ATSDR, 1997).

Detectable concentrations of dichlorobenzenes were found in adipose tissue and blood samples taken from Tokyo residents (Morita and Ohi, 1975; Morita et al., 1975). A national survey of various volatile organic chemicals demonstrated dichlorobenzenes in the three adipose tissues sampled. In addition, studies have shown that babies can receive dichlorobenzenes from mother's milk (ATSDR, 1997). Dichlorobenzenes are absorbed by experimental animals via inhalation, gavage, or subcutaneous injection (Hawkins et al., 1980). Data from oral administration of 1,4-dichlorobenzene to rabbits indicated oxidation to 2,5-dichlorophenol, which was found in the urine as a conjugate of glucuronic and sulfuric acids (Azouz et al., 1955). Other metabolites identified in the blood and urine of rats were 2,5-dichlorophenyl methyl sulfoxide and 2,5-dichlorophenyl methyl sulfone.

Severe hypochromic, microcytic anemia with excessive polychromasia, marginal nuclear hypersegmentation of the neutrophils, and a small number of red blood cells with Heinz bodies developed in a pregnant woman (21 years old) who consumed 1–2 blocks of 1,4-dichlorobenzene toilet air freshener per week throughout her pregnancy (Campbell and Davidson, 1970). A 19-year-old female who consumed 4–5 moth pellets containing 1,4-dichlorobenzene on a daily basis for 2.5 years developed symmetrical, well-demarcated areas of increased pigmentation over various parts of her body, which disappeared over a 4-month period after discontinuing the ingestion (Frank and Cohen, 1961).

In rats, 13-week gavage studies resulted in decreased hematocrit levels, red blood cell counts, and hemoglobin concentrations at 300 mg/kg/day (NTP, 1987). Oral administration of 1200 and 1500 mg/kg/day resulted in degeneration and necrosis of rat hepatocytes. Increased incidences of hepatocellular degeneration and individual cell necrosis were observed in male and female mice gavaged with 600–1800 mg/kg/day.

Rats exposed via inhalation to 96–341 ppm of 1,4-dichlorobenzene intermittently for 5–7 months had cloudy swelling and degeneration of hepatic parenchymal cells in the central zone of the liver. Increased liver weights in the male and/or female rats occurred above 96 ppm (Hollingsworth et al., 1956). During a 2-generation study, adult rats exposed to 538 ppm exhibited tremors, ataxia, and hyperactivity; decreased grooming behavior; and an unkempt appearance (Tyl and Neeper-Bradley, 1989). Both generations of offspring in the 538 ppm group had lower body weights at lactation day 4, and average litter size and survival were decreased. Selected animals from the first filial generation still had reduced body weights at 5 weeks post-exposure.

No epidemiologic studies or case reports addressing the carcinogenicity of 1,4-dichlorobenzene in humans were available. In a 2-year study, female rats and male and female mice were gavaged with 300 and 600 mg/kg/day and male rats were gavaged with 150 and 300 mg/kg/day (NTP, 1987). Nephropathy, epithelial hyperplasia of the renal pelvis, mineralization of the collecting tubules in the renal medulla, and focal hyperplasia of the renal tubular epithelium were noted in male rats receiving 150 and 300 mg/kg/day. Female rats gavaged with 300 and 600 mg/kg/day had an increased incidence of nephropathy and minimal hyperplasia of the renal pelvis or tubules. The following tumors were described as being present in the animals: renal tubular adenocarcinomas in male rats (controls, 2%; low dose, 6%; high dose, 14%), a marginal increase in mononuclear cell

leukemia in male rats (control, 10%; low dose, 14%; high dose, 22%), hepatocellular carcinomas in male mice (controls, 28%; low dose, 22.5%; high dose, 64%) and in female mice (controls, 10%; low dose, 10.4%; high dose, 38%), and hepatocellular adenomas in male mice (controls, 10%; low dose, 26.2%; high dose, 32%) and in female mice (controls, 20%; low dose, 12.5%; high dose, 42%). In this NTP study, the tumor incidence in female controls was higher than the historical control. In both male and female mice, hepatocellular degeneration with resultant initiation of tissue repair was present. These findings resulted in a speculation by NTP (1987) that 1,4-dichlorobenzene was acting as a tumor promotor for liver tumors in male and female mice.

Reference concentrations (RfC) of 2.5 mg/m^3 (0.42 ppm) for subchronic inhalation exposure (EPA 1995b) and 0.8 mg/m^3 (0.13 ppm) for chronic inhalation exposure for 1,4-dichlorobenzene were derived based on increased liver weights in the P1 males exposed via inhalation to 1,4-dichlorobenzene from the study of Tyl and Neeper-Bradley (1989). The No Observed Adverse Effects Level (NOAEL) was 301 mg/m^3 (50 ppm). The Lowest Observed Adverse Effects Level (LOAEL) was 902 mg/m^3 (150 ppm). 1,4-Dichlorobenzene has been classified as C, possible carcinogen to humans. For oral exposure, the slope factor was 0.024 $(mg/kg/day)^{-1}$, and the unit risk was 6.8E-7 $(\mu g/L)^{-1}$.

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Dichlorodifluoromethane

Dichlorofluoromethane (also known as Freon 12 or CFC-12) is a colorless, nonflammable gas with a characteristic ether-like odor. It is pressurized and used in liquid form as a refrigerant. It is also used as an aerosol propellant and in fire extinguishers (Sittig, 1991). Exposure to dichlorodifluoromethane may occur through inhalation and eye/skin contact.

At high inhalation doses in animals, dichlorodifluoromethane produces narcosis and asphyxiation. Surviving animals may exhibit lung tissue alterations. Lower levels of exposure result in tremors, liver injury, cardiac arrhythmias and airway constriction. Direct eye contact with the liquid form may result in freezing of the eye surface (ACGIH, 1991). In humans, inhalation of high doses results in narcosis, unconsciousness, cardiac arrhythmias, cardiac arrest and asphyxiation. Lower levels of exposure may result in generalized sensroy losses, ringing in the ears, apprehension and slurred speech. Contact with the liquid can cause pain, redness and frost bite because of the rapid evaporation of the chemical (Hathaway et al., 1991). No signs and symptoms have been associated with chronic, low-level exposures (Sittig, 1991). No information is available related to the carcinogenic potential of dichlorodifluoromethane.

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1,1-Dichloroethene

1,1-dichloroethene, also known as vinylidene chloride, is a chemical used to make certain plastics (such as packaging materials, flexible films like SARAN wrap) and flame retardant coatings

for fiber and carpet backing. It is a colorless liquid that evaporates quickly at room temperature. It has a mild sweet smell and burns quickly.

1,1-dichloroethene is a man-made chemical and is not found naturally in the environment. Although 1,1-dichloroethene is manufactured in large quantities, most of it is used to make other substances or products such as polyvinylidene chloride (ATSDR, 1994).

There is no data regarding the absorption, distribution or metabolism of 1,1-dichloroethene in humans. Studies in laboratory animals have demonstrated that 1,1-dichloroethene was rapidly absorbed following inhalation exposure (Dallas et al. 1983; McKenna et al. 1978a). Studies in animals clearly indicated that doses of 1,1-dichloroethene ranging from 10 to 100 mg/kg were rapidly and almost completely absorbed from the gastrointestinal tract of rats and mice following oral administration in corn oil (Jones and Hathway 1978a; Putcha et al. 1986). Although there is no information regarding the dermal absorption of 1,1-dichloroethene in animals, the physical/chemical properties of 1,1-dichloroethene indicate that dermal absorption of 1,1-dichloroethene is probable. 1,1-dichloroethene is a small organic molecule with properties similar to the lipid-soluble anesthetics. Thus, liquid 1,1-dichloroethene is expected to readily penetrate the skin, which is a lipid-rich tissue. However, with a vapor pressure of greater than 500 torr at room temperature, the rate of evaporation would be rapid leaving only a short time for skin penetration (ATSDR, 1994). Preferential accumulation of 1,1-dichloroethene was reported in the kidney and liver of rats exposed orally and via inhalation (Jaeger 1977, Jones and Hathway 1978b). The pathways of excretion are dose dependent regardless of oral or inhalation exposure. Administration of low doses results in the majority of the compound excreted as water soluble metabolites. As the dose increases and the metabolizing enzymes become saturated, more of the compound is excreted via exhalation (Jones and Hathway 1978b; McKenna et al. 1978a, 1978b; Reichert et al. 1979, Dallas et al. 1983).

Limited information is available on the human health effects following exposure to 1,1-dichloroethene. This information comes primarily from case reports and/or insufficiently detailed mortality studies wherein the concentration and duration of exposure to 1,1-dichloroethene were not quantified. Concurrent exposure to other toxic substances cannot be ruled out in most of these cases. Nevertheless, the information available indicates that relatively high concentrations of inhaled 1,1-dichloroethene can induce adverse neurological effects after acute-duration exposure (EPA, 1979b), and that 1,1-dichloroethene is associated with liver (Ott et al., 1976, EPA, 1976) toxicity in humans after repeated, low-level exposure.

Considerable information exists regarding the effects of 1,1-dichloroethene in animals after inhalation and oral exposure. The liver (Anderson and Jenkins, 1977, McKenna et al., 1978a, Anderson et al, 1978) and kidney (Jackson and Conolly 1985; Lee et al. 1977; McKenna et al. 1978a), and possibly the lungs (Gage 1970; Quast et al. 1986 Forkert et al. 1985), can be considered target organs for 1,1-dichloroethene by both routes of exposure. In addition, cardiovascular (Siletchnik and Carlson, 1974), neurological and developmental (Dawson et al. 1990, Short et al. 1977a, Murray et al. (1979) effects were reported after inhalation of 1,1-dichloroethene, and gastrointestinal effects occurred after oral exposure (Chieco et al.1981).

The RfD for 1,1-dichloroethene is based on liver toxicity (fatty changes) in a 2-yr chronic toxicity and carcinogenicity drinking water study conducted in rats (Quast, et al., 1983). Although this minimal effect might not be considered adverse—as there is no evidence of a functional change in the liver in rats exposed and glutathione levels are not reduced in this bioassay—the bench mark dose low ($BMDL_{10}$) was used to derive the RfD, because limiting exposure to the $BMDL_{10}$ will protect the liver from more serious damage (fatty liver or necrosis) that could compromise liver function. The duration adjusted $BMDL_{10}$of 4.6 mg/kg-day was divided by an uncertainty factor of 100 (10 each were used for interspecies extrapolation and intraspecies variability because there were no applicable data to justify departure from the default values) to arrive at a chronic RfD for 1,1-dichloroethene of 5E-02 mg/kg-day (IRIS, 2003).

The RfC for 1,1-dichloroethene is based on liver toxicity (fatty changes) in a chronic inhalation study in rats (Quast et al. 1986). Although this minimal effect might not be considered adverse—as there is no evidence of a functional change in the liver in rats exposed at this level and glutathione levels are not reduced—it is used to derive the RfC, because limiting exposure to this level will protect the liver from more serious damage (fatty liver or necrosis) that could compromise liver function. The duration adjusted NOAEL was used to calculate a human bench mark concentration low (BMCL) of 6.9 mg/m^3 which was divided by an uncertainty factor of 30 (a UF of 3 is used for interspecies extrapolation because a dosimetric adjustment was used. There is some suggestion that the effects in the kidney of male mice might occur at an exposure lower than the level that produced effects in the liver of rats. Thus, there is some uncertainty as to whether the most sensitive species has been used to derive the RfC. A UF of 10 is used for intraspecies variability because there were no applicable data to depart from the default value.) to arrive at a chronic RfC for 1,1-dichloroethene of 2E-01 mg/m^3 (USEPA, 2003).

1,1-dichloroethene was genotoxic in several in vitro test systems. A metabolic activation system is usually required for activity. Gene mutations were observed in bacteria, yeast, and plant cells (Bartsch et al. 1975, Bronzetti et al. 1981, Jones and Hathway 1978c, Van't Hof and Schairer 1982) and it induced gene conversion in yeast (Bronzetti et al. 1981; Koch et al. 1988). 1,1-dichloroethene was mutagenic in Salmonella after metabolic activation with an exogenous activation system derived from human liver cells (Jones and Hathway 1978c). In a mouse host-mediated assay system, 1,1-dichloroethene was mutagenic and induced gene conversion in yeast (Bronzetti et al.1981).

The carcinogenicity of 1,1-dichloroethene following inhalation, oral, dermal, and subcutaneous exposure has been evaluated in mice (Hong et al. 1981; Lee et al. 1978; Maltoni et al. 1985; Van Duuren et al. 1979) rats (Hong et al. 1981; Maltoni et al. 1985; Quast et al. 1983, 1986) and Chinese hamsters (Maltoni et al. 1985). Of the carcinogenicity bioassays conducted to date, only the results of a single inhalation study in mice by Maltoni et al. (1985) provide evidence of a positive carcinogenic effect from 1,1-dichloroethene exposure. In this study, increases in renal adenocarcinomas were noted in male Swiss mice exposed to 25 ppm 1,1-dichloroethene via inhalation. Mammary gland carcinomas and lung tumors, most of which were benign pulmonary adenomas, were also observed in this study.

The USEPA has classified 1,1-dichloroethene as a Group C carcinogen, possible human carcinogen.

EPA has concluded that 1,1-DCE exhibits *suggestive evidence* of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies in rodents and therefore has not developed an oral slope factor or an inhalation unit risk for this compound (IRIS, 2003). USEPA's HEAST document does provide an inhalation slope factor of 1.2 mg/kg-d^{-1} based upon adenocarcinomas in the kidneys of mice after a 12-month inhalation exposure (HEAST, 1997, Maltoni et al. 1985).

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1,1-Dichloroethene

1,1-Dichloroethene, also known as vinylidene chloride, is a chemical used to make plastics and flame retardant coatings. It is a colorless liquid that evaporates quickly at room temperature. It has a mild sweet smell and burns quickly.

1-1-Dichloroethene enters the environment when it is released to the air during its production, or released to surface water or soil as a result of waste disposal. Most 1,1-dichloroethene evaporates quickly and mainly enters the environment through the air, although some enters into rivers and lakes. In air, it breaks down quickly (half-life of 4 days). It tends to break down slowly in water. It is not readily transferred to fish or birds, and only very small amounts enter the food chain. In soil, 1,1-dichloroethene either evaporates or percolates through soil and enters groundwater. Bacteria in soil and groundwater slowly transform it into other lass harmful substances.

1,1-Dichloroethene easily enters the body through the lungs, if present in air, or through the stomach

and intestines, if contaminated materials are ingested. It can also penetrate through human skin. Following exposure, 1,1-dichloroethene partially leaves the body through the lungs. The remaining amount is broken down into other substances that then leave the body in urine within 1 to 2 days. Some of the breakdown products are more harmful than the parent compound.

Inhalation of high levels of 1,1-dichloroethene result in loss of breath and fainting. Prolonged inhalation exposures in humans and animals may result in adverse neurological effects and liver and kidney disease. Exposure of pregnant rats to 1,1-dichloroethene in air resulted in birth defects in the offspring. Oral exposures did not result in birth defects. Contact of 1,1-dichloroethene with skin and eyes can cause irritation.

The carcinogenic effects of 1,1-dichloroethene in humans is unknown. One study found that mice breathing 1,1-dichloroethene for one year developed kidney cancer. EPA has classified 1,1-dichloroethene as a group C carcinogen.

Agency for Toxic Substances and Dusease registry (ATSDR). 2002. Toxicological profile for 1,1-dichloroethene. U.S. Department of Health and Human Services.

1,2-Dichloroethene

1,2-Dichloroethene is a highly flammable, colorless liquid with a sharp, harsh odor. There are two isomers of 1,2-dichloroethene: cis- and trans-. Both forms may be present in a mixture, or the individual isomers may be used in their pure form. 1,2-Dichloroethene is used to produce solvents and in chemical mixtures. It enters the environment through industrial activity. It may be released from chemical factories during its manufacture, from landfills and hazardous waste sites, from chemical spills, from burning objects made of vinyl and from the breakdown of other chlorinated solvents.

1,2-Dichloroethene evaporates rapidly when exposed to air. It's half-life in air is 5 to 12 days. If present in soil, it may seep deeper into the soil and dissolve into groundwater. It's half-life in groundwater is 13 to 48 weeks. Small amounts of 1,2-dichloroethene may break down into vinyl chloride, a more hazardous chemical.

1,2-Dichloroethene enters the body through the lungs when contaminated air is breathed, through the stomach and intestines when contaminated food and water are ingested, or through the skin upon dermal contact with the chemical. Once absorbed, it rapidly distributes into blood and other tissues and is broken down into other compounds by the liver.

Inhalation of high levels of 1,2-dichloroethene can result in nausea, drowsiness, and fatigue. Higher levels can result in death. The lungs, liver and heart may be damaged after prolonged inhalation exposures. Oral doses have produced effects on the liver and blood (e.g., anemia). Animal studies suggest that exposure in utero may result in developmental delay. No studies have been done to determine the carcinogenic potential of 1,2-dichloroethene in humans or animals.

Agency for Toxic Substances and Dusease registry (ATSDR). 2002. Toxicological profile for 1,2-dichloroethene. U.S. Department of Health and Human Services.

Ethylbenzene

Ethylbenzene is a colorless liquid that smells like gasoline. It is volatile and flammable. Ethylbenzene occurs naturally in coal tar and petroleum. It is also found in many products, including paints, inks, and insecticides. Gasoline contains about 2% (by weight) ethylbenzene. Ethylbenzene is used primarily in the production of styrene. It is also used as a solvent, a component of asphalt and naphtha, and in fuels. In the chemical industry, it is used in the manufacture of acetophenone, cellulose acetate, diethylbenzene, ethyl anthraquinone, ethylbenzene sulfonic acids, propylene oxide, and α-methylbenzyl alcohol. Consumer products containing ethylbenzene include pesticides, carpet glues, varnishes and paints, and tobacco products. In 1994, approximately 12 billion pounds of ethylbenzene were produced in the United States. Ethylbenzene has a wide environmental distribution due to its widespread use (ATSDR, 1999).

Ethylbenzene has been shown to be readily absorbed via inhalation, ingestion, and dermal exposure in humans as well as in laboratory animals. Following exposure, ethylbenzene is distributed throughout the body, with the highest levels detected in the kidney, lung, adipose tissue, digestive tract, and liver (Chin et al., 1980). There appears to be quantitative differences in metabolism of the chemical in humans and laboratory animals. However, in all species, ethylbenzene undergoes a variety of microsomally mediated side-chain hydroxylations to yield the major metabolites, mandelic acid and phenylglyoxylic acid (Engstrom et al., 1984). The oxidation products are conjugated followed by urinary excretion, which appears to be complete within 2 days of exposure (ATSDR, 1999).

Humans exposed to low levels of ethylbenzene in air for short periods of time experience eye and throat irritation. Exposure to higher levels may cause more severe effects such as respiratory effects (irritation and chest constriction), central nervous system depression, decreased movement and dizziness, and more severe mucous membrane irritation. No studies have reported death in humans following exposure to ethylbenzene. No information was located to indicate that ethylbenzene produces toxicity in other organ systems upon short-term or prolonged exposure (ATSDR, 1999).

Animal studies indicate that the primary symptoms resulting from acute exposure to ethylbenzene are manifested as neurological and respiratory depression. Other studies suggest that the liver, kidney and hematopoietic system may also be targets of ethylbenzene toxicity (ATSDR, 1999). Studies indicate that ethylbenzene exposure of pregnant rats can produce fetotoxic effects at doses that also induce maternal toxicity (Andrew et al., 1981). Additionally, oral administration resulted in blockage of the estrus cycle in female rats (Ungvary, 1986). A NTP-sponsored 2-year bioassay revealed that male reproductive tissues may be a target for ethylbenzene toxicity (NTP, 1992).

The RfD for ethylbenzene is based on a 182 day oral bioassay conducted in rats (Wolf, et al., 1956). The duration adjusted NOAEL of 97.1 mg/kg-day for liver and kidney toxicity was divided by an uncertainty factor of 1000 (10 to account for interspecies differences; 10 for extrapolating from

subchronic to chronic exposure and 10 for protection of sensitive individuals) to arrive at a chronic RfD for ethylbenzene of 1E-01 mg/kg-day (IRIS, 2003).

The RfC for ethylbenzene is based upon a developmental study conducted in rats and rabbits (Andrew, et al., 1981). Developmental effects were selected as the critical effect for derivation of the RfC. The duration adjusted NOAEL was used to calculate a human equivalent concentration (HEC) of 434 mg/m^3 which was divided by an uncertainty factor of 300 (10 to protect sensitive humans; 3 to adjust for interspecies conversion; and 10 to adjust for the absence of multigenerational reproductive and chronic studies) to arrive at a chronic RfC for ethylbenzene of 1E+00 mg/m^3 (IRIS, 2003).

Results of in vitro genotoxicity test generally indicate that ethylbenzene is not mutagenic in the presence or absence of metabolic activation (ATSDR, 1999). In one in vivo study, there was no dose-dependent increase in the frequency of micronucleated polychromic erythrocytes (Mohtashamipur et al., 1985). Ethylbenzene did cause a mutagenic effect in mouse lymphoma cells and has been shown to induce a marginal yet significant increase in SCE in human lymphocytes. Therefore, ethylbenzene may cause an increased potential for genotoxicity in humans (ATSDR, 1999).

No association between increased cancer incidence in humans and exposure to ethylbenzene has been reported. In animal studies, the only chronic bioassay produced inconclusive results of the tumorigenicity of oral ethylbenzene (Maltoni et al., 1985).

The USEPA has classified ethylbenzene as a Group D carcinogen; not classifiable as to human carcinogenicity. The basis for this classification is due to lack of animal bioassays and human studies (IRIS, 2003).

Agency for Toxic Substances and Disease Registry (ATSDR) 1999. Toxicological Profile For Ethylbenzene. U.S. Public Health Service. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp110.html

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Ethylene Dibromide

Ethylene dibromide (1,2-Dibromoethane) is a pesticide and gasoline additive. It is mostly man-made, but it may occur naturally in the ocean in very small amounts. In the 1970s and early 1980s, it was used in soil to kill insects and worms that get on fruits, vegetables, and grain crops. It was also used in soil to protect grass, such as on golf courses. Another use was to kill fruit flies on citrus fruits, mangoes, and papayas after they were picked. EPA stopped most of these uses in 1984. Ethylene dibromide was added to leaded gasoline to produce better fuel efficiency. Because use of leaded gasoline has fallen, less ethylene dibromide is made for this use. The chemical is a colorless liquid with a mild, sweet odor. It evaporates easily and can dissolve in water (ATSDR, 1992).

There are no studies evaluating the absorption, distribution, metabolism or excretion of ethylene dibromide in humans. From the available data it appears that ethylene dibromide is absorbed via the inhalation, oral and dermal routes of exposure (Rowe et al. 1952; Stott and McKenna 1984, Botti et al. 1982; Nachtomi 1981; Plotnick et al. 1979; Van Bladeren et al. 1980, Jakobson et al. 1982). Indirect evidence in humans (intentional ingestion) indicates the distribution of ethylene dibromide to the kidneys and liver (Olmstead 1960; Saraswat et al. 1986). The tissue distribution of ethylene dibromide has been studied in rats following exposure by the oral route. Although retention was limited, the kidneys, liver, and spleen appear to retain the highest amounts of the administered dose (Plotnick et al. 1979). Ethylene dibromide is metabolized to active forms capable of inducing toxic effects by either of two systems- -the microsomal monooxygenase system (cytochrome P-450 oxidation) (Tamura et al. 1986; Van Duuren et al. 1985) and the cytosolic activation system (glutathione conjugation) (Peterson et al. 1988). Oral administration of 1,2-dibromoethane to rats primarily results in mercapturic acid derivatives excreted in the urine (approximately 74% of the administered dose) (Plotnick et al. 1979). Unmetabolized 1,2-dibromoethane may be excreted via the lungs; fecal excretion of metabolites accounts for approximately 3% of the administered dose (Plotnick et al. 1979).

Humans are susceptible to the acute toxic effects of 1,2-dibromoethane from various routes of exposure. Except for adverse reproductive effects in men after occupational exposure, chronic effects of 1,2-dibromoethane exposure have not been documented in humans. Based on data derived from animal studies, mechanisms of action of 1,2-dibromoethane at a cellular level, toxicokinetics, and genotoxicity tests, there is a potential for certain adverse health effects in humans exposed chronically to low environmental levels of 1,2-dibromoethane that could exist near hazardous waste sites or areas of former agricultural use. Clinical signs in humans related to acute toxic exposure to 1,2-dibromoethane are depression and collapse, indicative of neurologic effects, and erythema and necrosis of tissue at the point of contact (oral and pharyngeal ulcers for ingestion, skin blisters and sloughing for dermal exposure). Target organs of 1,2-dibromoethane are of two types. The first is the point of contact with the chemical, i.e., skin for dermal exposure, oropharynx for ingestion and upper respiratory tract for inhalation exposure. Although there is little information on toxicity of 1,2-dibromoethane in humans after inhalation, the testis was a target organ in exposed workers; the liver and kidney have been identified as target organs after dermal and oral exposure in humans (ATSDR, 1992).

The liver, kidney, and testis are target organs in experimental animals irrespective of the exposure route. The respiratory tract is a target organ after inhalation exposure due to point of contact exposure. Subchronic inhalation of 1,2-dibromoethane (Nitschke et al. 1981) resulted in hyperplasia of nasal turbinate epithelium at the mid and high doses; rats at the highest dose also exhibited nonkeratinizing squamous metaplasia of respiratory epithelium of the nasal turbinates. The liver is a target organ for toxic effects of 1,2-dibromoethane following exposure by a variety of routes (Botti et al. 1986; Brandt et al. 1987; Broda 1976; NTP 1982). 1,2-Dibromoethane, as well as inducing necrosis, can also act as a hepatocellular mitogen in rats (Ledda-Columbano et al. 1987). Following chronic inhalation exposure to 1,2-dibromoethane, rats developed toxic nephropathy (NTP 1982). 1,2-Dibromoethane can be activated in the kidney of rodents by a glutathione-dependent pathway to toxic metabolites, as well as having such metabolites reach the kidney via the enterohepatic circulation (Rush et al. 1984; Working et al. 1986).

In rats and mice exposed to 1,2-dibromoethane by inhalation, most developmental effects have been observed at doses that produced maternal toxicity (Short et al. 1978, 1979). The available data from animal studies indicate that the male reproductive system in rats is affected by exposure to 1,2-dibromoethane at high doses (atrophy of the testis, epididymis, prostate, and seminal vesicles)(Short et al. 1979, NTP, 1982).

Neither IRIS (2003) nor HEAST (1997) has a verifiable chronic oral RfD for ethylene dibromide.

IRIS does not have a chronic inhalation RfC for ethylene dibromide. US EPA's HEAST (HEAST, 1997) presents a chronic RfC for ethylene dibromide based upon sperm effects in humans (Ratcliffe, et al., 1987, Schrader et al., 1988). The LOAEL of 88 ppb and the uncertainty factor of 1000 were used to arrive at a chronic RfC for ethylene dibromide of 2E-04 mg/m^3 (HEAST, 1997).

1,2-Dibromoethane has been tested extensively to assess its genotoxic potential in prokaryotic, eukaryotic, and mammalian systems. The results of these studies indicate that 1,2-dibromoethane is

a potent mutagen, producing a broad spectrum of mutations in various test systems. In bacterial systems, 1,2-dibromoethane is a direct-acting mutagen and primarily causes mutations of the base-pair substitution type (Barber et al. 1981; McCann et al. 1975; Moriya et al. 1983; Principe et al. 1981; Rosenkranz 1977). 1,2-dibromoethane has been shown to bind covalently to DNA both in vitro (Banerjee and Van Duuren 1979, 1986; DiRenzo et al. 1982) and in vivo (Hill et al. 1978; Inskeep et al. 1986; Koga et al. 1986; Prodi et al. 1986), forming a stable adduct.

There are no reports of cancer in humans associated with occupational exposure to 1,2-dibromoethane, although the negative epidemiologic studies have some limitations. 1,2-dibromoethane has been positive in short-term tests in animals used to predict carcinogenic potential of a chemical (Milks et al. 1982; Moslen 1984). In addition, there is dramatic tissue-specific binding of metabolites in experimental animals. 1,2-dibromoethane is a potent carcinogen in rats and mice, causing malignant and benign neoplasms of epithelial and mesenchymal origin in multiple organ systems when administered by inhalation, oral, or dermal routes. Cancer was also induced at initial point of contact with 1,2-dibromoethane--nasal cavity for inhalation exposure, forestomach for oral (gavage and drinking water) exposure, and skin for dermal exposure (NTP, 1982, NCI, 1978, Van Duuren et al. 1979).

The EPA has classified ethylene dibromide as a Group B2 carcinogen; probable human carcinogen based upon increased incidences of a variety of tumors in rats and mice in both sexes by three routes of administration at both the site of application and at distant sites. Ethylene dibromide is mutagenic in various in vitro and in vivo assays. Ethylene dibromide is structurally similar to dibromochloropropane, a probable human carcinogen and to ethylene dichloride, a probable human carcinogen (IRIS, 2003). The oral slope factor for ethylene dibromide is 8.5E+1 $(mg/kg\text{-}d)^{-1}$ based upon squamous cell carcinoma of the forestomach in rats. The inhalation unit risk factor for ethylene dibromide is 2.2E-04 $(ug/m^3)^{-1}$ and is based upon nasal cavity tumors (including adenoma, adenocarcinoma, papillary adenoma, squamous cell carcinoma, and or/papilloma) (IRIS, 2003).

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Isopropylbenzene

Isopropylbenzene, also known as cumene, is a potent narcotic and a primary skin and eye irritant. It is an aromatic organic solvent (much like toluene or xylene) and is found most commonly as a component of hydrocarbon fuels (e.g., gasoline).

Isopropylbenzene is absorbed efficiently from the respiratory tract . It is absorbed through intact

skin more rapidly than other aromatic solvents. After absorption, isopropylbenzene is widely distributed with most of the parent compound undergoing biotransformed. Breakdown products are excreted via urine within 40 hours of exposure.

No human information on the toxicity of this compound was located. However, neurotoxicological effects from long-term exposure to isopropylbenzene would be expected. Upon short-term, high level exposure, animals exhibited damage to the spleen and fatty changes to the liver, but no renal or pulmonary effects (Sandmeyer, 1981). Long-term gavage exposure results in a slight increase in liver weight in rats (Wolf at al., 1956). Short-term exposures result in transient symptoms typical of central nervous system depression. No indications of developmental toxicity were noted in inhalation studies in which pregnant rats and rabbits were exposed to isopropylbenzene vapors.

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Methylcyclohexane

Methylcyclohexane is a component of fuels and has similar toxicity to the straight chain hydrocarbons of similar size (e.g., hexane). It is a liquid at room temperature, but will volatilize to air with relative ease. Methylcyclohexane is a six-membered aliphatic ring compound with a single methyl-substitution. In humans, methylcyclohexane can produce central nervous system depression upon low level inhalation exposures, and dermal irritation following skin contact.

Limited quantitative toxicity information in laboratory animals is available for this compound. A one-year inhalation study in rats demonstrated mineralization and papillary hyperplasia in affected kidneys. A NOAEL was identified as 287 mg/m^3. This study serves as the basis for the inhalation RfC (HEAST, 1997).

Health Effects Assessment Summary Tables (HEAST). 1997. Environmental Protection Agency. Solid Waste and Emergency Response. EPA-540-R-97-036. July 1997.

Methyl tert-butyl ether

Methyl *tert*-butyl ether (MTBE) occurs as a colorless liquid and is used as an octane booster in unleaded gasoline. In city areas where there are concerns over pollutants like carbon monoxide, EPA may require the use of MTBE or ethanol as an oxygenating agent to make the fuel burn more cleanly during the winter months. Fuels containing these additives are called reformulated gasolines (ATSDR, 1996). MTBE is also used in the manufacture of isobutene (HSDB, 2003; Merck, 1989).

The general population may be exposed to MTBE via the inhalation of air contaminated from its use as an octane booster or a pollution reducer in unleaded gasoline, ingestion of food or water

contaminated with MTBE or by dermal contact. Workers may be occupationally exposed via inhalation or dermal contact (ATSDR, 1996). Acute (short-term) exposure of humans to MTBE has occurred via injection into the gallbladder during its use as a medical treatment to dissolve cholesterol gallstones. Nausea, vomiting, and sleepiness have been observed; in one case renal failure was reported (HSDB, 2003). Acute inhalation exposure has resulted in ataxia and abnormal gait in rats. Acute animal tests, such as the LC_{50} and LD_{50} test in rats, have demonstrated MTBE to have low acute toxicity via inhalation and moderate acute toxicity via ingestion (RTECS, 1993).

No information is available on the chronic (long-term) health effects of MTBE in humans. Increased liver and kidney weights, decreased brain weight, swollen periocular tissue, and ataxia have been reported in rats following chronic inhalation exposure. Increased severity of spontaneous renal lesions and increased prostration (lying flat or exhaustion) were reported in females only. Increased liver, kidney, spleen, and adrenal weights; ataxia; and decreased brain weight, body weight, and body weight gain have been observed in mice chronically exposed to MTBE by inhalation. Increased prostration was reported in females (HSDB, 2003).

No information is available on the reproductive or developmental toxicity of MTBE in humans. In rats exposed via inhalation, reduced body weight and body weight gain in pups and decreased pup viability have been reported. A decreased number of viable implantations, increased maternal toxicity, dead fetuses, late resorptions, and skeletal variations have been reported in mice exposed via inhalation (HSDB, 2003).

A RfD for MTBE is not available on IRIS at this time (IRIS, 2003). The NCEA has developed a provisional RfD for MTBE of 8.6E-01 mg/kg/day as cited in the Region IX PRG Tables (USEPA, 2002).

The RfC for MTBE is based on increased liver and kidney weights, increased prostration in females, and swollen periocular tissues in male and female rats (Chun, et al., 1992). The duration adjusted NOAEL was used to calculate a human equivalent concentration (HEC) of 259 mg/m^3 was divided by an uncertainty factor of 100 (an uncertainty factor of 10 is applied to account for extrapolation to sensitive human subpopulations, an additional factor of 3 is used to account for interspecies extrapolation. A full 10-fold adjustment for interspecies extrapolation is not deemed necessary due to the use of dosimetric adjustments. An uncertainty factor of 3 is applied for data base deficiencies because of the lack of certain information from the chronic exposure bioassay (e.g., urinalysis results, serum chemistry, and limited reporting of motor activity/clinical signs during exposure)) to arrive at a chronic RfC for MTBE of 3 mg/m^3 (IRIS, 2003). Information on the genotoxicity of MTBE indicates that it has little if any genotoxic activity (ATSDR, 1996).

Available carcinogenicity studies indicate the MTBE can produce tumors in multiple species of animals, multiple strains of rats, and at multiple sites, the relevance of the carcinogenic effects of MTBE to humans is of concern. However, the NTP, EPA, and International Agency for Research on Cancer (IARC) have not yet classified MTBE as to its carcinogenicity potential for humans (ATSDR, 1996, IRIS, 2003). The NCEA has developed an oral slope factor of 3.3E-03 $(mg/kg/day)^{-1}$ and an inhalation slope factor of 3.5E-04 $(mg/kg/day)^{-1}$ (USEPA, 2002)

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Methylene Chloride

Methylene chloride, also known as dichloromethane, is a colorless volatile liquid with a penetrating ether-like odor. In industry, methylene chloride is widely used as a solvent in paint removers, degreasing agents, and aerosol propellants; as a polyurethane foam-blowing agent; and as a process solvent in the pharmaceutical industry. The compound is also used as an extraction solvent for spice oleoresins, hops, and caffeine (ATSDR, 2000; IARC, 1986).

Methylene chloride is readily absorbed from the lungs, the gastrointestinal tract, and to some extent through the skin. Metabolism of methylene chloride produces CO_2 and CO, which readily binds with blood hemoglobin to form carboxyhemoglobin (CO-Hb). The primary adverse health effects associated with methylene chloride exposure are central nervous system (CNS) depression and mild liver effects. Neurological symptoms described in individuals occupationally exposed to methylene chloride included headaches, dizziness, nausea, memory loss, paresthesia, tingling hands and feet, and loss of consciousness (Welch, 1987). Major effects following acute inhalation exposure include fatigue, irritability, analgesia, narcosis, and death (ATSDR, 2000). CNS effects have also been demonstrated in animals following acute exposure to methylene chloride (Weinstein et al., 1972; Berger and Fodor, 1968).

Impaired liver function has been associated with occupational exposure to methylene chloride (Welch, 1987). Liver effects have also been documented in a number of inhalation studies with laboratory animals. Subchronic exposure of rats, mice, dogs, and monkeys caused mild hepatic effects such as cytoplasmic vacuolization and fatty changes (USEPA, 1983; Haun et al., 1972; Weinstein and Diamond, 1972; Heppel, 1944). Hepatocellular foci, fatty changes, and necrosis were reported following chronic inhalation exposure of rats and mice (Nitschke et al., 1988a; NTP, 1986). Chronic oral exposure to methylene chloride via drinking water resulted in histopathological alterations of the liver in rats and mice (NCA, 1982, 1983). In addition, inhalation exposure of rats caused nonspecific degenerative and regenerative changes in the kidneys (USEPA, 1983; Haun et al., 1972).

The RfD for methylene chloride is based on a 2-year study conducted in rats (NCA, 1982). This value is based on a NOAEL of 5.85 mg/kg/day divided by an uncertainty factor of 100 (the 100-fold factor accounts for both the expected intra- and interspecies variability to the toxicity of this chemical in lieu of specific data) to arrive at a chronic RfD for methylene chloride of 6E-2 mg/kg/d) (IRIS, 2003).

A RfC for methylene chloride is not available on IRIS (2003) at this time. A RfC for methylene chloride is available in HEAST (1997) and is based on a 2 year inhalation study in rats (Nitschke, et al., 1988a). The RfC is based upon a NOAEL of 694.8 mg/m^3 divided by an uncertainty factor of 100 (the 100-fold factor accounts for both the expected intra- and interspecies variability to the toxicity of this chemical in lieu of specific data) to arrive at a chronic RfC for methylene chloride of 3 mg/m^3 (HEAST, 1997).

Studies of workers exposed to methylene chloride have not recorded a significant increase in cancer cases above the number of cases expected for nonexposed workers (Hearne et al., 1987; Ott et al., 1983a; Friedlander et al., 1978). However, long-term inhalation studies with rats and mice demonstrated that methylene chloride causes cancer in laboratory animals. Mice exposed via inhalation to high concentrations of methylene chloride (2000 or 4000 ppm) exhibited a significant increase of malignant liver and lung tumors compared with nonexposed controls (NTP, 1986). Rats of both sexes exposed to concentrations of methylene chloride ranging from 500 to 4000 ppm showed increases of benign mammary tumors (Nitschke et al., 1988a; NTP, 1986; Burek et al., 1984). An inhalation study with rats and hamsters revealed sarcomas of the salivary gland in male rats, but not in female rats or hamsters (Burek et al., 1984). Liver tumors observed in rats and mice that ingested methylene chloride in drinking water for 2 years provided suggestive evidence of carcinogenicity (NCA, 1982, 1983).

EPA has classified methylene chloride as a B2; probable human carcinogen. This classification is based on inadequate human data and sufficient evidence of carcinogenicity in animals; increased incidence of hepatocellular neoplasms and alveolar/bronchiolar neoplasms in male and female mice, and increased incidence of benign mammary tumors in both sexes of rats, salivary gland sarcomas in male rats and leukemia in female rats. This classification is supported by some positive genotoxicity data, although results in mammalian systems are generally negative. A slope factor and unit risk of

7.5E-3 $(mg/kg/day)^{-1}$ and 2.1E-7 $(ug/L)^{-1}$, respectively, was derived for oral exposure to methylene chloride. The inhalation unit risk is 4.7E-7 $(ug/m^3)^{-1}$(IRIS, 2003).

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Tetrachloroethene

Tetrachloroethene (PCE) is readily absorbed following inhalation and oral exposure (ATSDR 1992). Tetrachloroethene vapors and liquid also can be absorbed through the skin (USEPA 1985a,b). Humans acutely exposed to tetrachloroethene at levels as low as 216 mg/m^3 experienced respiratory irritation, dizziness, and sleepiness (Rowe et al. 1952). The principal toxic effects of tetrachloro-ethene in humans and animals following acute and longer-term exposures in-clude CNS depression and fatty infiltration of the liver and kidney with concomitant changes in serum enzyme

activity levels indicative of tissue damage (U.S. EPA 1985a,b; Buben and O'Flaherty 1985). Mice subchronically exposed to tetrachloroethene did not show any adverse liver effects at 20 mg/kg/day (Buben and O'Flaherty 1985). Humans exposed to doses of between 136 and 1,018 mg/m^3 for 5 weeks develop CNS effects, such as lassitude and signs of inebriation (Stewart et al. 1974). The offspring of female rats and mice exposed to high concentrations of tetrachloroethene (300 mg/m^3) for 7 hours daily on days 6 to 15 of gestation developed toxic effects, including a decrease in fetal body weight in mice and a small but significant increase in fetal resorption in rats (Schwetz, Leong, and Gehring 1975). Mice also exhibited develop-men-tal effects, including subcutaneous edema and delayed ossification of skull bones and sternebrae (Schwetz, Leong, and Gehring 1975). In an NCI (1977) bioassay, increased incidence of hepatocellular carcinoma were observed in both sexes of B6C3F1 mice administered tetrachloroethylene (386–1,072 mg/kg/day) in corn oil by gavage for 78 weeks. Increased incidence of mononuclear cell leukemia and renal adenomas and carcinomas (combined) have also been observed in long-term bioassays in which rats were exposed to tetrachloroethene by inhalation at air concentrations of 200–400 mg/m^3 (NTP 1986).

Tetrachloroethene is currently under review by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) and estimates of cancer potency were recently withdrawn by USEPA (1995). However, the USEPA National Center for Environmental Assessment (USEPA 1996a) currently classifies tetrachloroethene as a Group B2/C carcinogen (Probable/Possible Human Carcinogen). USEPA (1996a) has reported an oral slope factor of 5.2×10^{-2} $(mg/kg/day)^{-1}$ based on liver tumors observed in the NCI (1977) gavage bioassay for mice. The cancer slope factor is currently under review by USEPA. USEPA (1996b) has also derived an oral RfD of 1×10^{-2} mg/kg/day for tetrachloroethene based on a 6-week gavage study by Buben and O'Flaherty (1985). In this study, liver weight/body weight ratios were significantly increased in mice and rats treated with 71 mg/kg/day tetrachloroethene but not in animals treated with 14 mg/kg/day. Using a NOAEL of 14 mg/kg/day and applying an uncertainty factor of 1,000 the RfD was derived.

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Toluene

Toluene is a clear, colorless organic liquid with a sweet smell and a high degree of lipid solubility. It is used as an industrial solvent/degreaser, as an intermediate in the manufacture of chemicals and pharmaceuticals, and is present as a component of gasoline and other fuels, paints, lacquers, adhesives, rubber and printing ink. Toluene is a volatile molecule with relatively low water solubility. It is flammable and may pose a fire hazard if handled improperly (ATSDR, 2000).

Toluene is readily absorbed by all routes of exposure. Once absorbed, it is rapidly distributed to all organ systems, including fetal tissue, with highest concentrations occurring in organs with high lipid content such as adipose tissue, brain and bone marrow. Toluene undergoes primarily oxidative metabolism to benzyl alcohol mediated by the mixed function oxidase enzyme system. Benzyl alcohol is further oxidized by alcohol and aldehyde dehydrogenase to produce benzoic acid, which is primarily conjugated with glycine or glucuronic acid and excreted in urine as hippuric acids or benzoyl glucuronide. Toluene may also be excreted unchanged in exhaled air. Metabolism and excretion occurs rapidly, with the major portion occurring within 12 hours of exposure (ATSDR, 2000).

In humans, the most profound effects of toluene are on the central nervous system. Acute exposure results in reversible depression of the central nervous system, neurological dysfunction, impaired performance and narcosis. Chronic exposure has been reported to result in permanent central nervous system effects such as ataxia, tremors and impaired speech, hearing and vision (ATSDR, 2000). Toluene vapors cause irritation of the upper respiratory tract, mucous membranes and eyes, and may produce cardiac arrhythmias upon chronic exposure (Anderson et al., 1982). Reports of effects on the hematological system, liver, kidney, immune system, reproductive organs and the developing fetus are confounded by exposure to multiple solvents (ATSDR, 1989). Case reports of birth defects in children of mothers who abused toluene during pregnancy suggest that exposure to high levels of toluene may be toxic to the developing fetus. However, results from animal studies indicate that toluene is not a teratogenic agent, but can retard fetal growth and skeletal development and adversely influence behavior of offspring at exposure levels that overwhelm maternal mechanisms protecting the developing fetus from exposure (ATSDR, 2000).

Toluene has been demonstrated to produce similar effects in humans and animals. The major target organ following acute or chronic exposure is the central nervous system. Signs of central nervous system damage include impaired motor abilities, narcosis, tremors, alterations in EEG activity, changes in the levels of brain neurotransmitters and morphological effects (ATSDR, 1989). High-level inhalation exposure resulted in respiratory irritation and inflammation and pulmonary lesions (NTP, 1989). Toluene does not appear to be directly toxic to the cardiovascular system (Bruckner and Peterson, 1981). Decreased leukocyte counts were observed in dogs following exposure to toluene (Hobara et al., 1984). In addition, exposed mice exhibited increased susceptibility to respiratory infection (Aranyi et al., 1985). Hepatic effects appear to be relatively mild with reported increases in liver weight and minor ultrastructural changes (Ungvary et al., 1982). Renal toxicity has not been observed (NTP, 1989; Bruckner and Peterson, 1981). Studies with animals provide evidence that toluene may be a developmental toxicant. Exposure in utero resulted in skeletal anomalies, retarded skeletal growth and low fetal weights (Ungvary, 1985). No reproductive effects have been reported (API, 1985; NTP, 1989).

The RfD for toluene is based on a 13-week subchronic gavage study conducted in rats (NTP, 1989). The duration adjusted NOAEL of 223 mg/kg-day for changes in liver and kidney weights was divided by an uncertainty factor of 1000 (10 to account for intra and interspecies differences; 10 for extrapolating from subchronic to chronic exposure and 10 for limited reproductive and developmental exposure data) to arrive at a chronic RfD for toluene of 2E-01 mg/kg-day (IRIS,

2003).

The RfC for toluene is based upon occupational study of exposed females in a glue factory (Foo, et al., 1990). Neurological effects were selected as the critical effect for derivation of the RfC. The duration adjusted NOAEL was used to calculate a human equivalent concentration (HEC) of 119 mg/m^3 for neurobehavioral effects was divided by an uncertainty factor of 300 (10 to protect sensitive humans; 10 to extrapolate from a LOAEL to a NOAEL; and 3 for database deficiencies, including the lack of data and well-characterized laboratory animal exposures evaluating neurotoxicity and respiratory irritation) to arrive at a chronic RfC for toluene of 4E-1 mg/m^3 (IRIS, 2003).

Available in vitro studies suggest that toluene is nongenotoxic (ATSDR, 1989). In vivo studies in animals provide additional supportive evidence (API, 1981). A small number of human studies have reported an increased incidence in chromosomal abnormalities; however, these studies are confounded by possible co-exposure to other chemicals (Schmid et al., 1985; Bauchinger et al., 1982). Other human studies have found no correlation between exposure to toluene and increased frequencies of chromosomal abnormalities (Haglund et al., 1980; Maki-Paakkanen et al., 1980).

Human and animal studies generally do not support a concern for the carcinogenicity of toluene. The only available human epidemiological studies were negative but inconclusive due to limitations in design. The validated animal inhalation bioassays were negative (CIIT 1980; NTP 1990); however, one available oral study showed a nondose-related increase in a variety of tumors (Maltoni et al. 1997). Thus, the data do not support a firm conclusion regarding the carcinogenicity of toluene.

The USEPA has classified toluene as a Group D carcinogen; not classifiable as to human carcinogenicity. The basis for this classification is a lack of human data, inadequate animal data and predominantly negative results in the majority of genotoxic assays (IRIS, 2003).

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1,2,4-Trichlorobenzene

1,2,4-Trichlorobenzene usually present in a mixture of three trichlorobenzene isomers and has been used as a solvent in the manufacturing of chemicals, dyes & intermediates, dielectric fluid, synthetic transformer oils, lubricants, heat-transfer medium, and insecticides (Lewis, 1993). It is also used in degreasing agents, septic tank and drain cleaners, wood preservatives, and abrasive formulations (McNamara, et al, 1981).

All three isomers of trichlorobenzene are absorbed from the GI tract, intact skin, and lung (USEPA, 1980). After oral administration of radioactively labeled 1,2,4-trichlorobenzene, the bladder, kidney, fat, skin, liver, and adrenals, showed high 1,2,4-trichlorobenzene activity up to 24 hr post treatment (Chu, et al., 1987). Lingg, et al., (1980) demonstrated that there is a sharp distinction between the types of conjugates formed by rats and rheusus monkeys. Glucuronide conjugates and unconjugated trichlorophenols comprised the majority of the urinary metabolites after oral and i.v. administration of 1,2,4-trichlorobenzene to rheusus monkeys. Cysteine conjugates and isomers of trichlorothiophenol comprised the majority of the urinary metabolites after oral and i.v. administration of 1,2,4-trichlorobenzene to rats.

There is limited information regarding the human toxicity of 1,2,4-trichlorobenzene. Industrial experience has shown this compound to be a skin, eye and throat irritant. There is the potential for trichlorobenzene induced hepatic toxicity in situations where exposures to high concentrations are encountered (ACGIH, 1992).

Male rats, rabbits and beagle dogs were exposed to 0, 30, or 100 ppm of 1,2,4-trichlorobenzene for 7 hr/day, 5 days/week for 30 exposures in 44 days. In all 3 species there were no significant effects on body weight gain, hematologic and serum biochemical tests or gross and histopathologic appearance of tissues. At 100 ppm 1,2,4-trichlorobenzene**,** both rats and dogs had increased liver weights, and the rats also had increased relative kidney weight. Urinary excretion of porphyrins increased in rats exposed to 30 or 100 ppm 1,2,4-trichlorobenzene**,** most likely as a result of hepatic microsome induction (Kociba, et al. 1981).

Possible maternal and hepatic reproductive effects of 1,2,4-trichlorobenzene were assessed in rats given 0, 36, 120, 360, and 1200 mg/kg/day on days 9-13 of gestation. Animals were sacrificed on day 14 of pregnancy. Although pretreatment with 360 mg/kg/day did not increase resorptions, embryolethality, or teratogenicity, embryonic development was significantly retarded by all 4 growth criteria used (head length, crown-rump length, somite number, and protein content) (Kitchin and Ebron, 1983). In a multigeneration reproductive study, litters (17-23 litters/dose group) of the F0 generation were randomly reduced to 4 males and 4 females at birth. Male and female progeny were dosed with 0, 25, 100 or 400 ppm of 1,2,4-trichlorobenzene in the drinking water. The study

ended when the F2 generation was 32 days old. Fertility (as indexed by conception rate of dams) of the F0 and F1 generation rats was not affected by treatment. A LOAEL was derived from a significant increase (11% in males, 13% in females) in adrenal gland weights observed in the 400-ppm groups of males and females of the F0 and F1 generations (Robinson, et al., 1980).

The RfD for 1,2,4-trichlorobenzene is based on a multigeneration reproductive study conducted in rats (Robinson, et al., 1980). The critical effect on which the RfD is based is increased adrenal weights and vacuolization of zona fasciculate in the cortex. The NOAEL of 14.8 mg/kg-day was divided by an uncertainty factor of 1000 (10 was used to account for extrapolation from laboratory studies to humans. An additional factor of 10 was used to allow for sensitive subpopulations among humans. An additional factor of 10 was used to account for a lack of chronic studies) to arrive at a chronic RfD for 1,2,4-trichlorobenzene of 1E-02 mg/kg-day (IRIS, 2003).

An RfC for 1,2,4-trichlorobenzene is not available on IRIS (2003) at this time. However, USEPA's HEAST document provides a chronic RfC of 2E-01 mg/m^3. The RfC is based upon a inhalation study conducted in rats, rabbits, dogs and monkeys exposed to 1,2,4-trichlorobenzene for 6 and 26 weeks (Kociba, et al., 1981; Coate, et al., 1977; Cote, et al., 1988). The NOEL of 104 ppm is based upon non-adverse liver weight changes. An uncertainty factor of 1000 was applied to this NOEL to obtain the RfC (HEAST, 1997).

1,2,4-Trichlorobenzene was evaluated for mutagenicity and hepatic enzyme induction potential in the Salmonella microsomal assay. The compound did not revert strains TA1535, TA1537, TA98, or TA100 when tested with or without metabolic activation at seven or eight concentrations over a three-log dose range (Schoeny, et al., 1979; Lawlor, et al., 1979).

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Trichloroethene

Absorption of trichloroethene (TCE) from the gastrointestinal tract is virtually complete. Absorption following inhalation exposure is proportional to concentration and duration of exposure (USEPA, 1985). TCE is a CNS depressant following acute and chronic exposures. In humans, single oral doses of 15–25 mL (21–35 grams) have resulted in vomiting and abdominal pain, followed by transient unconsciousness (Stephens, 1945). High-level exposure can result in death due to respiratory and cardiac failure (ATSDR, 1995). Hepatotoxicity has been reported in human and animal studies following acute exposure to TCE (ATSDR, 1995). Nephrotoxicity has been observed in animals following acute exposure to TCE vapors (ACGIH, 1986; Torkelson and Rowe, 1981). Subacute inhalation exposures in mice have resulted in transient increased liver weights (Kjellstrand *et al*., 1983a,b). Industrial use of TCE is often associated with adverse dermatological effects including reddening and skin burns on contact with the liquid form, and dermatitis resulting

from vapors. These effects are usually the result of contact with concentrated solvent. However, no effects have been reported following exposure to TCE in dilute, aqueous solutions (USEPA, 1985). TCE has caused significant increases in the incidence of hepatocellular carcinomas in mice (NCI, 1976), renal tubular-cell neoplasms in rats exposed by gavage (NTP, 1983), and pulmonary adenocarcinomas in mice following inhalation exposure (Fukuda *et al*., 1983; Maltoni *et al*., 1986). TCE was mutagenic in *Salmonella typhimurium* and in *E. coli* (strain K-12), utilizing liver microsomes for activation (Greim *et al*., 1977).

USEPA is currently reviewing the carcinogenicity of TCE. The National Center for Environmental Assessment (NCEA) currently classifies TCE as a Group B2/C (Probable/Possible Human Carcinogen) based on inadequate evidence in humans and sufficient evidence of carcinogenicity from animal studies. NCEA (USEPA, 1998) reports a provisional oral cancer slope factor of 1.1×10^{-2} $(mg/kg\text{-}day)^{-1}$ based on two gavage studies conducted in mice in which an increased incidence of liver tumors were observed (Maltoni *et al*., 1986; Fukuda *et al*., 1983). The cancer estimate is currently under review by USEPA.

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1,1,1-Trichloroethane

1,1,1-Trichloroethane (also known as 1,1,1-TCA) is a colorless man-made chemical. It can be found in a liquid state, vapor, or dissolved in water or other chemicals. When found as a liquid, it evaporates rapidly and becomes a vapor in the air. 1,1,1-TCA has a sweet, sharp odor (ATSDR, 1990). 1,1,1-Trichloroethane is often used as a solvent to dissolve other substances such as glue or paint. Industrially, it is used to remove oil or grease from manufactured metal parts. Residentially, it is used for spot removal cleaners, aerosol sprays and glues. 1,1,1-Trichloroethane can be found in hazardous waste sites in the soil, water and in the air (ATSDR, 1990). It can be found in rivers, lakes, soil, drinking water, and drinking water from underground wells.

1,1,1-Trichloroethane is rapidly and completely absorbed by ingestion and inhalation (ATSDR, 1995). It distributes throughout the body and crosses the blood-brain barrier (ATSDR, 1995). 1,1,1-TCA is absorbed through human skin. The amount of 1,1,1-trichloroethane absorbed depended on the surface area of exposed skin and the method of exposure (i.e., immersion or topical application). 111-TCA appears to preferentially distribute to fatty tissues (ATSDR, 1995). Regardless of how 1,1,1-trichloroethane enters the body, most will quickly leave as exhalation occurs (ATSDR, 1990). What does not exit from expiration (metabolites) will be excreted through the urine and breath in a few days.

The toxic effects of 1,1,1-TCA are generally seen at concentrations well above those likely in an ambient environment. The most notable toxic effects of 1,1,1-TCA in humans are central nervous system depression, including anesthesia at very high concentrations, and impairment of coordination, equilibrium, and judgment at lower concentrations. Exposure to high concentrations may also result in cardiovascular effects, including premature ventricular contractions, decreased blood pressure and sensitization of the heart to epinephrine-induced arrhythmias, leading possibly to cardiac arrest (U.S. EPA, 1985; ATSDR, 1990). Acute exposure to minimal concentrations of 1,1,1-

trichloroethane did not produce respiratory or lung volume effects (Dornette, 1960; Torkelson et al., 1958).

Similar effects as noted above are observed in animals exposed to 1,1,1-TCA. In addition, animal experiments investigating the influence of 1,1,1-TCA on liver and kidney function yield conflicting results highly dependent on species, doses, and treatment schedules. Fatty changes in rodent livers following exposure by inhalation have been reported (U.S. EPA, 1985).

Neither developmental effects nor adverse effects of 1,1,1-trichloroethane on reproduction in humans have been reported. Histological evaluation of reproductive organs and tissues from rats and mice of either sex revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). However, testicular degeneration was observed in guinea pigs (Adams et al. 1950). Minor embryotoxic effects were observed in rats and rabbits after inhalation exposure to high concentrations of 1,1,1-trichloroethane (BRRC 1987a, 1987b; York et al. 1982). Effects included decreased fetal weights, increased minor soft tissue and skeletal anomalies, and delayed ossification. The developmental defects reported in two of these studies (BRRC 1987a, 1987b) may have been associated with significant maternal toxicity.

Neither IRIS nor HEAST carry verified toxicity values such as an RfD or RfC for 1,1,1-TCA.

Due to the lack of adequate oral toxicity data pertaining to sensitive effects and species of 1,1,1-TCA the NCEA Superfund Technical Support Center derived the provisional RfD using inhalation data. The provisional RfD is based on a 12-month inhalation study in rats (Quast et al. 1978). Hepatotoxicity was selected as the critical effect for derivation of the RfD. The RfD was derived using physiologically based pharmacokinetic modeling to arrive at a provisional RfD of 2.8 E-1 mg/kg-d (NCEA, 1999a).

The NCEA Superfund Technical Support Center has derived a provisional RfC for 1,1,1-TCA. The provisional RfC is based on a 3-month inhalation study in gerbils (Rosengren et al., 1985). Increased glial fibrillary acidic (GFA) protein indicating brain astrogliosis in gerbils was selected as the critical effect for derivation of the RfC. The RfC was derived using physiologically based pharmacokinetic modeling to arrive at a provisional RfC of 2.2 mg/m^3 (NCEA, 1999b).

The genotoxic effects of 1,1,1-trichloroethane have been studied, extensively. Although most tests of mutagenicity in the Ames *Salmonella* assay produced negative results, those conducted in a desiccator, to minimize evaporation and maximize exposure were mostly positive (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977). These results indicate that 1,1,1-trichloroethane may be mutagenic in *Salmonella.* The results were negative in other tests of genotoxicity in bacteria and fungi. Although 1,1,1-trichloroethane was mutagenic in a few assays with *Salmonella,* induced chromosomal aberrations in a Chinese hamster ovary cell assay, and was positive in most mammalian cell transformation assays, the existing genotoxicity data are largely negative. In addition, positive results may have been produced by stabilizers and not 1,1,1-trichloroethane itself. Therefore, a firm conclusion regarding the genotoxic potential of 1,1,1-

trichloroethane in humans is not possible (ATSDR, 1995).

A relationship between exposure to 1,1,1-trichloroethane and cancer in humans has not been established. Animal studies fail to provide any definitive link between exposure and carcinogenicity (ATSDR, 1995).

The USEPA has classified 1,1,1-TCA as a Group D carcinogen; not classifiable as to human carcinogenicity. The basis for this classification is that there are no reported human data and animal studies (one lifetime gavage, one intermediate-term inhalation) have not demonstrated carcinogenicity. Technical grade 1,1,1-trichloroethane has been shown to be weakly mutagenic, although the contaminant, 1,4-dioxane, a known animal carcinogen, may be responsible for this response (IRIS, 2003).

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Trimethylbenzene

Trimethylbenzene is a clear, colorless liquid with a pleasant aromatic odor. All three isomers of trimethylbenzene are present in petroleum and coal tar. The isomers of trimethylbenzene are used as raw materials in chemical syntheses and as ultraviolet stabilizers, e.g., in plastics. They are present in many high-boiling hydrocarbon solvents, especially those enriched in aromatics (ACGIH, 1992). 1,2,4-Trimethylbenzene and 1,3,5-Trimethylbenzene, also known as pseudocumene and mesitylene, respectively, have been identified to be pharmacologically and toxicologically similar (Gerarde, 1960).

Trimethylbenzenes have been shown to accumulate in adipose tissue in both humans and rats following both inhalation and oral exposure (Jarnberg, et al., 1996, Jarnberg, et al., 1997, Zahlsen, 1990, Hou, et al., 1989). In humans exposed to trimethylbenzenes via inhalation, approximately 20 to 37% of the dose was cleared by exhalation. Urinary excretion of the compounds amounted to less than 0.002% of the dose. The authors concluded that the trimethylbenzene isomers are rapidly absorbed following inhalation exposure and metabolized at a moderately rapid rate. The low urinary excretion rate indicates that extensive accumulation of the compounds in adipose tissue occurs (Jarnberg, et al., 1996, Jarnberg, et al., 1997). Rats given single oral doses of 1,2,4-trimethylbenzene exhibited rapid distribution throughout the body, with highest levels in adipose tissue. No evidence was obtained of any of the other organs or tissues having preferential uptake. The tissue levels declined rapidly within 24 hours after dosing, with more than 99 percent of the administered radioactivity being recovered in the urine in this period of time. More than 81 percent of the administered dose was accounted for in the urine by a complex mixture of isomeric trimethylphenols, dimethylbenzyl alcohols, dimethylbenzoic acids, and dimethylhippuric acids. The major metabolites identified were 3,4-dimethylhippuric-acid, 2,4-dimethylbenzylalcohol, and 2,5-dimethylbenzyl-alcohol (Hou, et al., 1989).

Studies indicated that these compounds enter the body primarily through inhalation but can also be absorbed through the skin. Pneumonitis, edema, tissue necrosis and hemorrhage of the lungs have been brought about by the aspiration of liquid trimethylbenzenes. The use of an organic solvent containing 50 percent pseudocumene, 30 percent mesitylene, and traces of hemimellitene caused hypochromic anemia, hemopoietic disturbances, chronic asthmatic bronchitis, and central nervous system depression in humans (Anon. 1981).

Subchronic inhalation exposure of 1,2,4-trichlorobenzene to rats resulted in some disturbances in hematological parameters characterized by decrease in red and increase in white blood cells at the high concentration of 1230 mg/m^3. Pulmonary lesions observed in male and female rats were

statistically significant at mid and high concentrations of 1,2,4-trichlorobenzene (Korsak et al., 2000). Exposure of rats to each of the trimethylbenzene isomers in a subchronic inhalation study resulted in concentration-dependent neurological disturbances such as a decrease in rotarod performance and decrease in pain sensitivity in rats. Two weeks after cessation of inhalation exposure to pseudocumene or hemimellitene no recovery in rotarod performance behavior was observed (Korsak and Rydzynski, 1996). No information was found on chronic, developmental or reproductive toxicity.

Neither IRIS nor HEAST carry verified toxicity values such as an RfD or RfC for the trimethylbenzenes. The NCEA has developed a provisional oral and inhalation RfDs for 1,2,4-trimethylbenzene and 1,3,5-trimethylbenzene. The oral RfD for both isomers is 5E-02 mg/kg-d while the inhalation RfD for both isomers is 1.7E-03 mg/kg-d as cited in the Region IX PRG Tables (USEPA, 2002).

The three trimethyl isomers of benzene (hemimellitene, 1,2,3-TMB; pseudocumene, 1,2,4-TMB and mesitylene, 1,3,5-TMB) were investigated for different genotoxicity endpoints: in vitro, in the Ames test with Salmonella typhimurium TA97a, TA98, TA100 and TA102 strains in the presence and absence of rat liver S9 metabolic activation; in vivo, in the micronucleus and sister chromatid exchange (SCE) tests with bone marrow cells of Imp:Balb/c mice. Only the isomer of benzene with the methyl-group at positions 1, 2, and 3 was found to have mutagenic effect on S. typhimurium cells. Increase in bacterial reversions was observed in four conventional strains used in this study, but most clearly in TA97a. The mutagenic responses of 1,2,3-TMB with the Salmonella tester strains were observed in the experiments performed in the absence of enzymatic activation. None of the compounds had an influence on the frequency of micronucleated polychromatic erythrocytes in bone marrow cells of mice (Janik-Spiechowicz, et al., 1998).

Neither IRIS nor HEAST carry verified toxicity values such as oral slope factors and inhalation unit risk values.

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1,1,2-Trichloroethane

1,1,2-Trichloroethane is a colorless, sweet-smelling liquid that does not burn easily and boils at a higher temperature than water (ATSDR, 1989). 1,1,2-Trichloroethane is an intermediate in the production of vinylidene chloride, and is used as a solvent and component of adhesives (IARC, 1972).

Studies in humans indicate that 1,1,2-trichloroethane is absorbed rapidly after inhalation exposure (Morgan et al, 1970, 1972). No studies were located regarding absorption in humans following oral or dermal exposure to 1,1,2-trichloroethane (ATSDR, 1989). Studies in animals indicate that 1,1,2-trichloroethane is absorbed following inhalation, oral and dermal exposure (Filser et al. 1982; Mitoma et al. 1985; Jakobson et al. 1977; Tsuruta 1975). Little information is available on the distribution of 1,1,2-trichloroethane in humans or animals. Data in animals suggest distribution to fat and to the liver in animal models (Takahara 1986, Mitoma et al. 1985). The primary metabolites

identified in rats and mice given 1,1,2-trichloroethane by gavage were chloroacetic acid, S-carboxymethylcysteine, and thiodiacetic acid (Mitoma et al. 1985). S-carboxymethycysteine and thiodiacetic acid are formed from 1,1,2-trichloroethane following conjugation with glutathione (Yllner 1971). Chloroacetic acid is formed by hepatic cytochrome P-450 (Ivanetich and Van Den Honert 1981).Cytochrome P-450 can also produce free radicals from 1,1,2-trichloroethane (Mazzullo et al. 1986). Little is known about the excretion of 1,1,2-trichloroethane in humans. The excretion routes were shown to be similar in rats and mice, regardless of whether the chemical was given orally (Mitoma et al. 1985) or intraperitoneally (Yllner et al. 1971). The majority of 1,1,2-trichloroethane was found as metabolites in the urine, followed by exhalation as the second route of excretion (Yllner et al. 1971).

Other than studies on dermal irritation, no studies were located regarding health effects in humans following inhalation, oral, or dermal exposure to 1,1,2-trichloroethane; therefore, all implications for public health are derived from animal studies (ATSDR, 1989).

1,2-Trichloroethane had adverse effects the liver (Gehring 1968, Tyson et al. 1983, White et al. 1985), kidneys (Plaa et al. 1958, Wright and Schaffer 1932), immune system (Sanders et al. 1985), and central nervous system (Gehring 1968, De Ceaurriz et al.1981) in animal models.

The RfD for 1,1,2-trichloroethane is based on effects on erythrocytes and depressed humoral immune status in a subchronic toxicity and drinking water study conducted in rats (Sanders, et al., 1985; White, et al., 1985). The NOAEL of 3.9 mg/kg-day was divided by an uncertainty factor of 1000 (which includes the standard uncertainty factors for interspecies and intrahuman variability, and a factor of 10 for extrapolation to lifetime exposure from an intermediate exposure duration) to arrive at a chronic RfD for 1,1,2-trichloroethane of 4E-03 mg/kg-day (IRIS, 2003).

Neither IRIS (IRIS, 2003) nor HEAST (HEAST, 1997) include a verifiable chronic inhalation RfC for 1,1,2-trichloroethane.

It is evident that 1,1,2-trichloroethane does have some genetic effects both in vitro and in vivo. In vitro mutagenicity assays were negative in Salmonella typhimurium (Simmon et al. 1977) and positive in Saccharomyces cerevisiae (Bronzetti et al. 1987). A cell transformation assay performed in the absence of activation on mouse BALB/c-3T3 cells was negative (Tu et al. 1985). A test of DNA repair in cultured rat hepatocytes was positive, but one in mouse hepatocytes was not (Williams 1983).

There is no evidence for carcinogenicity of 1,1,2-trichloroethane in humans. Among animals, 1,1,2-trichloroethane was carcinogenic in B6C3Fl mice, but not Osbourne-Mendel rats. In a gavage study by NCI (1978), this compound produced significant increases in the incidence of hepatocellular carcinomas and adrenal pheochromocytomas in mice.

The USEPA has classified 1,1,2-trichloroethane as a Group C carcinogen; possible human carcinogen. This classification is based upon hepatocellular carcinomas and pheochromocytomas in one strain of mice. Carcinogenicity was not shown in rats. 1,1,2-Trichloroethane is structurally

related to 1,2-dichloroethane, a probable human carcinogen (IRIS, 2003). The oral slope factor of 5.7E-02 mg/kg-d^{-1} is based upon hepatocellular carcinomas in mice following oral exposure (NCI, 1978). The inhalation unit risk value of 1.6E-05 $(ug/m^3)^{-1}$ is based upon route-to route extrapolation from the oral slope factor.

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Vinyl Chloride

Vinyl chloride, a colorless gas, is a halogenated aliphatic hydrocarbon with the empirical formula of C_2H_3Cl. It is used primarily as an intermediate in the manufacture of polyvinyl chloride (PVC); limited quantities are used as a refrigerant and as an intermediate in the production of chlorinated compounds (ATSDR, 1989).

Vinyl chloride is rapidly absorbed from the gastrointestinal tract and lungs. Metabolism of vinyl chloride occurs primarily in the liver via oxidation by hepatic microsomal enzymes to polar compounds which can be conjugated with glutathione and/or cysteine. These covalently bound metabolites are then excreted in the urine (U.S. EPA, 1980, 1985).

In humans and animals, vinyl chloride is a CNS depressant, inducing narcosis and anesthesia at high concentrations (Torkelson and Rowe, 1981; Patty et al., 1930). Nonneoplastic toxic effects observed in workers exposed by inhalation to vinyl chloride include hepatotoxicity, acroosteolysis and scleroderma, and Raynaud's syndrome, a vascular disorder of the extremities. Also reported were abnormalities of CNS function, high blood pressure, and occasional pulmonary effects (ATSDR, 1989; U.S. EPA, 1985; Lloyd et al., 1984; Langauer-Lewowicka et al., 1983; Waxweiler et al., 1977). The evidence for potential developmental effects in humans (increased fetal loss and birth defects) is equivocal (ATSDR, 1989; Waxweiler et al., 1977; Infante et al., 1976). Occupational exposure to vinyl chloride has been associated with reduced sexual function in both sexes and gynecological effects in women (Makarov, 1984; Makarov et al., 1984).

For the oral route of exposure, the primary target organ of vinyl chloride toxicity in animals is the liver. Chronic oral administration of 1.7-14.1 mg/kg/day of vinyl chloride induced dose-related increases in nonneoplastic lesions of the liver of rats (Feron et al., 1981). In addition to the CNS, target organs for inhalation exposure include the liver, kidneys, lungs, spleen, and testes. Subchronic inhalation studies with rodents documented hepatic effects at concentrations as low as 50 ppm (Sokal et al., 1980) and degenerative changes of the liver and kidneys at >= 500 ppm (Torkelson et al., 1961). Exposure to higher concentrations caused proliferative changes in the lungs of mice (Suzuki, 1980), extensive liver and kidney damage in rats and guinea pigs, cerebral and cerebellar nephrosis in rats, and degeneration of the spleen in guinea pigs (Prodan et al., 1975; Viola, 1971). Subchronic exposure of rats to 100 ppm vinyl chloride produced significantly decreased testes weights and testicular regeneration (Bi et al., 1985). Evidence of developmental toxicity was seen in rats exposed to vinyl chloride during the first trimester of gestation (Ungvary et al., 1978).

The carcinogenicity of vinyl chloride in humans has been demonstrated in a number of epidemiological studies and case reports, many of which associated occupational exposure to vinyl chloride to the development of angiosarcomas of the liver. In addition to liver cancer, exposure to vinyl chloride also has been linked to an increased risk of lung, brain, hematopoietic, and digestive tract cancers (U.S. EPA, 1985; Heldaas et al., 1984; IARC, 1979; Byren et al., 1976; Waxweiler et al., 1976; Monson et al., 1974). Vinyl chloride has been shown to be carcinogenic in numerous animal studies. Inhalation exposure to vinyl chloride induced an increased incidence of liver angiosarcomas; kidney nephroblastomas; and lung, brain, and forestomach tumors in rodents

(Maltoni et al., 1980, 1981; Feron et al., 1981; Hong et al., 1981; Suzuki, 1978; Lee et al., 1977, 1978). Oral administration of vinyl chloride induced liver, lung, and kidney tumors in rodents (Feron et al., 1981; Maltoni, 1977). Angiosarcomas observed in offspring of rats exposed by inhalation during gestation indicates that vinyl chloride has the potential to initiate cancer *in utero* (Radike et al., 1988). EPA has classified vinyl chloride as a Group A chemical, human carcinogen (U.S. EPA, 1985).

Xylenes

Xylenes are colorless liquid organic molecules with a sweet odor and a high degree of lipid solubility. There are three isomers of xylene: meta- ortho- and para-xylene (m-, o- and p-xylene, respectively). The term "total xylenes" is used to designate a mixture of the three possible isomers, in any proportions. They are commonly used as industrial solvents, as components of paints, varnishes, cleaners, degreasers and gasoline and as chemical intermediates in the manufacture of other chemicals, plastics and synthetic fibers. Xylenes are volatile molecules and therefore, evaporate quickly. They are also flammable and may pose a fire hazard if handled improperly (ATSDR, 1995).

Xylenes are readily absorbed by all routes of exposure. Xylenes are very soluble in blood and therefore are absorbed easily into the systemic circulation during exposure (Astrand, 1982). Following absorption, distribution occurs rapidly to all organs, including fetal tissue, with greatest distribution occurring to organs having a high lipid content, such as adipose tissue, bone marrow and brain (Astrand, 1982; Engstron and Bjurstrom, 1978; Riihimaki et al., 1979). In humans, xylenes are primarily metabolized by the mixed function oxidase enzyme system in the liver to methylbenzyl alcohols that are further oxidized by alcohol and aldehyde dehydrogenase to yield methyl benzoic acids. The acids are readily conjugated and excreted in urine (Fishbein, 1985). In addition, a small percentage (3-6%) is exhaled unchanged due to the volatile nature of these compounds.

Human data suggests that the three xylene isomers all produce qualitatively similar effects, although the individual isomers are not necessarily equal in potency with regard to a given effect (ATSDR, 1995). Exposure, by any route, results in primarily central nervous system effects that may include headaches, nausea, mental confusion, narcosis, impaired learning and memory, dizziness, tremors, unconsciousness and coma, depending on dose and length of exposure. High doses may result in death. The respiratory system may also be a target of xylene toxicity in humans, producing respiratory tract irritation, pulmonary edema and inflammation after inhalation. Ocular irritation may result following exposure to xylene vapors. Skin irritation, dryness and scaling may result following dermal exposure. Limited data are available concerning effects of exposure on the hepatic, renal, cardiovascular, musculoskeletal or hematological system. Insufficient information is available regarding the developmental and reproductive toxicity of xylenes in humans (ATSDR, 1995)

Exposure to xylenes produces similar effects in humans and laboratory animals. The central nervous system is the primary target for both short-term and long-term exposures. Respiratory effects are observed following inhalation exposure. Data from animal studies provide limited evidence that

xylene may produce cardiovascular effects (arrhythmias, atrial fibrillation and alterations in blood vessels and blood flow) (Morvai et al., 1976, 1987), hepatic effects (enzyme induction, increased liver weight, ultrastructural alterations) (Condie et al., 1988; Elovaara et al., 1980; Elovaara, 1982) and renal effects (enzyme induction, renal atrophy, tubular alterations) (Condie et al., 1988; Elovaara, 1982; Toftgard and Nilsen, 1982). These results suggest that humans might be at increased risk of developing such effects following exposure.

Although the human data regarding the developmental effects of xylene suggest a possible relationship between solvent (unspecified) exposure and developmental toxicity (Holmberg and Nurminen 1980; Kucera 1968; Taskinen et al. 1989; Windham et al. 1991), these data are limited for assessing the relationship between inhalation of xylene and developmental effects because the available studies involved concurrent exposure to other solvents in addition to xylene in the workplace (Holmberg and Nurminen 1980; Kucera 1968; Taskinen et al. 1989; Windham et al. 1991) and because of the small number of subjects ranging from 9 to 61 (Taskinen et al. 1989; Windham et al. 1991).

Findings in animal studies suggest that xylenes may produce developmental defects including increased fetal death, decreased fetal weight, delayed skeletal development and gross anomalies (Marks et al., 1982; Ungvary et al., 1980). No animal data exists suggesting effects on reproductive organs, the musculoskeletal system or hematological system.

The RfD for xylenes is based on a 2-year study conducted in rats (NTP, 1986). The duration-adjusted NOAEL of 179 mg/kg-day for decreased body weight gain 5 –8 % of controls) in male rats was divided by an uncertainty factor of 1,000 (10 to extrapolate from rats to humans; 10 to protect sensitive humans and 10 for database deficiencies, including the lack of adequate studies of the oral neurotoxicity of xylenes as well as multigenerational reproductive toxicity and developmental neurotoxicity studies) to arrive at a chronic RfD for xylenes of 2E-1 mg/kg-day (IRIS, 2003).

Because available human data are insufficient for derivation of an RfC and chronic animal inhalation data are lacking, the subchronic study by Korsak et al. (1994) was selected as the principal study. Neurological effects (impaired motor coordination) were selected as the critical effect for derivation of the RfC. The duration adjusted NOAEL was used to calculate a human equivalent concentration (HEC) of 39 mg/m^3 for neurobehavioral effects was divided by an uncertainty factor of 300 (3 to extrapolate from rats to humans; 10 to protect sensitive humans; 3 to extrapolate from a subchronic to a chronic study; and 3 for database deficiencies, including the lack of a two-generation reproductive toxicity study and chronic inhalation data) to arrive at a chronic RfC for xylenes of 1E-1 mg/m^3 (IRIS, 2003).

Xylenes have been tested for genotoxicity in a variety of in vitro and in vivo assays. Results of the various assays indicate that xylenes are nongenotoxic following in vitro and in vivo exposure (ATSDR, 1995). No evidence of carcinogenicity exists in humans or laboratory animals (ATSDR, 1995).
Under the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), *data are inadequate for an assessment of the carcinogenic potential* of xylenes. Adequate human data on the

carcinogenicity of xylenes are not available, and the available animal data are inconclusive as to the ability of xylenes to cause a carcinogenic response. Evaluations of the genotoxic effects of xylenes have consistently given negative results (USEPA, 2003).

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SEMI-VOLATILE

Acetophenone

Acetophenone occurs as a colorless liquid that is slightly soluble in water (USEPA, 1987; HSDB, 2003; Merck, 1989). Acetophenone is used in perfumery as a fragrance ingredient in soaps, detergents, creams, lotions, and perfumes; as a flavoring agent in foods, nonalcoholic beverages, and tobacco; as a specialty solvent for plastics and resins; as a catalyst for the polymerization of olefins; and in organic syntheses as a photosensitizer (USEPA, 1987; HSDB, 2003; Merck, 1989).

Occupational exposure to acetophenone may occur during its manufacture and use (Sittig, 1985). Acetophenone has been detected in ambient air and drinking water; exposure of the general public may occur through the inhalation of contaminated air or the consumption of contaminated water (USEPA, 1987). Hippuric acid may be monitored in the urine to determine whether or not exposure to acetophenone has occurred (Sittig, 1985).

Acute (short-term) exposure of humans to acetophenone vapor may produce skin irritation and transient corneal injury. One study noted a decrease in light sensitivity in exposed humans (USEPA, 1987; HSDB, 2003). Acute oral exposure has been observed to cause hypnotic or sedative effects, hematological effects, and a weakened pulse in humans (Sittig, 1985; HSDB, 2003). Congestion of the lungs, kidneys, and liver were reported in rats acutely exposed to high levels of acetophenone via inhalation (HSDB, 2003). Tests involving acute exposure of animals, such as the LD_{50} test in rats, mice, and rabbits, have demonstrated acetophenone to have moderate acute toxicity from oral or dermal exposure (RTECS, 1993).

No information is available on the chronic (long-term) effects of acetophenone in humans. Degeneration of olfactory bulb cells was reported in rats chronically exposed via inhalation. In another study, chronic inhalation exposure of rats produced hematological effects and, at high doses, congestion of cardiac vessels and pronounced dystrophy of the liver (USEPA, 1987; HSDB, 1993). In two studies, no effects were observed in rats chronically exposed to acetophenone in their diet (USEPA, 1987; HSDB, 2003).

No information is available on the reproductive or developmental effects of acetophenone in humans. In one study of pregnant rats exposed dermally, no effects on reproduction or development were noted (USEPA, 1987; HSDB, 2003).

The RfD for acetophenone based on a subchronic study in rats (Hagen et al., 1967). The adjusted NOAEL of 423 mg/kg-day for general toxicity was divided by an uncertainty factor of 3,000 (10 to extrapolate from rats to humans; 10 to protect sensitive humans, 10 to extrapolate from a subchronic study to a chronic study and 3 for database deficiencies, including the lack of reproductive toxicity developmental studies) to arrive at a chronic RfD for acetophenone of 1E-1 mg/kg-day (IRIS, 2003).

There is no RfC for acetophenone at this time (IRIS, 2003).

No information is available on the carcinogenic effects of acetophenone in humans or animals. EPA has classified acetophenone as a Group D, not classifiable as to human carcinogenicity (IRIS, 2003).

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1,1-Biphenyl

Chronic exposure to 1,1-biphenyl is characterized by central nervous system effects, fatigue, headache, tremors, insomnia, sensory impairment accompanied by clinical findings of cardiac and hepatic impairment, irregularities of the peripheral and central nervous system and possible brain lesions (Sandmeyer, 1981). A feeding study in rats resulted in kidney damage, reduced hemoglobin levels, decreased food intake and decreased longevity (Ambrose et al, 1960).

Limited teraotgenicity data indicate that 1,1-biphenyl is not teratogenic. Some evidence of fetotoxicity has been noted following high-dose exposure to pregnant laboratory animals.

Based on a lack of human carcinogenicity data and inadequate studies in laboratory animals, 1,2-biphenyl is classified as a Group D carcinogen (i.e., not classifiable) by EPA. This compound was not mutagenic in reverse mutation testing and in a DNA repair test. 1,1-Biphenyl did induce forward mutations in mouse lymphoma cells and sister chromatid exchanges in Chinese hamster cells, although a dose-response relationship was not observed (EPA, 2003).

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4-Methylphenol

4-Methylphenol (p-cresol) belongs to the cresol family. Three types of closely related cresols exist: ortho-cresol (o-cresol), meta-cresol (m-cresol), and para-cresol (p-cresol). Pure cresols are colorless chemicals, but they may be found in brown mixtures such as creosote and cresylic acids (e.g., wood preservatives). Because these three types of cresols are manufactured separately and as mixtures, they can be found both separately and together. Cresols can be either solid or liquid, depending on how pure they are; pure cresols are solid, while mixtures tend to be liquid. Cresols are natural products that are present in many foods and in animal and human urine. They are also present in wood and tobacco smoke, crude oil, and coal tar. In addition, cresols also are man-made and used as disinfectants and deodorizers, to dissolve substances, and as starting chemicals for making other chemicals (ATSDR, 1992).

No studies were located regarding the rate and extent of absorption in humans following inhalation and oral exposure to cresols. The occurrence of coma, death, and systemic effects in two humans dermally exposed to cresols (Cason 1959; Green 1975) indicates that these compounds can be absorbed through the skin. No studies were located that sought to quantify the rate or extent of absorption in intact humans. An in vitro study of the permeability of human skin to cresols found that these substances had permeability coefficients greater than that for phenol, which is known to be readily absorbed across the skin in humans (Roberts et al. 1977). There is limited information regarding the rate and extent of absorption in animal models following inhalation, oral and dermal exposure. It is known that cresol can be absorbed after inhalation due to mortality and other effects seen in animal studies (Campbell 1941; Kurlyandsky et al. 1975). Rabbits orally exposed to cresols excreted 65% to 84% of the administered dose in the urine (Bray et al., 1950). No studies were located regarding the distribution of cresols after oral, inhalation and dermal exposure in humans or animals. No studies were located regarding metabolism in humans following exposure to cresols. A few studies reported on the metabolism of cresols in animals. Cresols in the urine are found primarily as sulfate and glucuronide conjugates (Bray et al., 1950).

Effects reported in humans include mucosal irritation following inhalation; mouth and throat burns, abdominal pain, vomiting, tachycardia and ventricular fibrillation, hemolytic anemia, and impaired kidney function following ingestion of highly concentrated solutions; and hemolytic anemia, anuria, elevated blood urea levels, and severe skin corrosion following spilling of highly concentrated solutions on the skin (ATSDR, 1992).

Data from animal studies generally support the portal of entry effects reported in humans, such as mucosal irritation following inhalation, gastrointestinal irritation following oral administration, and severe skin damage following dermal application. Other effects, such as hemolytic anemia, have not been reported in animals; however, the doses given in the animal studies that examined toxic effects to the blood are probably well below those to which the humans were exposed. Other acute effects reliably reported to occur in animals include labored breathing, ocular discharge, and reduced body weight gain. In rats, oral exposure to 4-methylphenol produced reductions in body weight gain and occasional organ weight changes as well as some more notable changes, such as an increased incidence of epithelial metaplasia in the trachea, mild reductions in hemoglobin, hematocrit and red blood cell counts, increased serum transaminase levels (indicative of liver damage and associated with liver inflammation in this study), and mild nephropathy (ATSDR, 1992).

No developmental effects have been reported in humans exposed to cresols. Slightly elevated incidences of minor variations in rats and rabbits exposed 4-methylphenol at maternally toxic doses indicate that this chemical is a weak developmental toxicant capable of producing mild fetotoxic effects in these species (BRRC 1988, 1989). No reproductive effects have been reported in humans exposed to cresols. No adverse reproductive effects were seen even at parenterally toxic doses in two-generation studies in rats (BRRC 1988, BRRC 1989).

The Oral RfD for 4-methylphenol was withdrawn from IRIS on 08/01/1991 as a result of further review. A new RfD summary is in preparation by the RfD/RfC Work Group (IRIS, 2003). EPA's HEAST (HEAST, 1997a) provides a chronic RfD of 5E-03 mg/kg-d, which is based upon a developmental study in rabbits (CMA, 1988). The uncertainty factor applied to the NOAEL is 1000.

Neither IRIS nor HEAST carry an RfC for 4-methylphenol. The health effects data for 4-methylphenol were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for the derivation of an inhalation RfC. The verification status for this chemical is currently not verifiable (IRIS, 2003).

The genotoxic effects of cresols have been well studied. 4-metholphenol produced chromosomal aberrations in Chinese ovary cells (Hazleton Labs 1988a), but did not produce sister chromatid exchange in in vitro or in vivo assays by Cheng and Kligerman (1984). 4-methylphenol also produced cell transformation in mouse BALB/C-3T3 cells (Hazleton Labs, 1988b) and a minor increase in DNA synthesis in human peripheral lymphocytes in vitro (Daugherty and Franks 1986).

Studies found no relationship between endogenous 4-methylphenol levels in the urine and the occurrence of large bowel cancer (Bone et al. 1976) or bladder cancer (Renwick et al. 1988) in humans. There are no data available regarding the carcinogenicity of exogenous cresols in humans. No cancer bioassays have been conducted in animals, but the results of a promotion study in mice suggested that cresols could be cancer promoters (Boutwell and Bosch 1959).

The USEPA has classified 4-methylphenol as a Group C carcinogen; possible human carcinogen. The basis for this classification is due to an increased incidence of skin papillomas in mice in an

initiation-promotion study. The three cresol isomers produced positive results in genetic toxicity studies both alone and in combination. A quantitative estimate of carcinogenic risk from oral or inhalation exposure to 4-methylphenol has not been conducted (IRIS, 2003).

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BRRC. 1989. Bushy Run Research Center. Two-Generation Reproduction Study of p-Cresol (CAS No. 106-44-5) Administered By Gavage To Sprague-Dawley (CD®) Rats. Project report 52-512. Unpublished data submitted to The Chemical Manufacturers Association Cresols Panel, Washington, DC. As cited in ATSDR, 1992.

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CMA (Chemical Manufacturer's Association). 1988. Developmental Toxicity Evaluation of o-, m-, or p-Cresol Administered By Gavage to New Zealand White Rabbits. Final Project Report. 51-508. Fiche No. OTS0517695. As cited in HEAST, 1997).

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SEMI-VOLATILE – POLYCYCLIC AROMATIC HYDROCARBONS

Polycyclic Aromatic Hydrocarbons (Carcinogenic)

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

PAH absorption following oral and inhalation exposure is inferred from the demonstrated toxicity of PAHs following ingestion and inhalation, respectively (USEPA, 1984a). PAHs are also absorbed following dermal exposure (Kao *et al*., 1985). It has been suggested that simultaneous exposure to carcinogenic PAHs (cPAHs) such as benzo(a)pyrene and particulate matter can increase the effective dose of the compound (ATSDR, 1995). Acute effects from direct contact with PAHs and related materials are limited primarily to phototoxicity; the primary effect is dermatitis (NIOSH, 1977). PAHs have also been shown to cause cytotoxicity in rapidly proliferating cells throughout the body; the hematopoietic system, lymphoid system, and testes are frequent targets (Santodonato *et al*., 1981). Destruction of the sebaceous glands, hyperkeratosis, hyperplasia, and ulceration have been observed in mouse skin following dermal application of the cPAHs (Santodonato *et al*., 1981). Benzo(a)pyrene has also been shown to have an immunosuppressive effect in animals (ATSDR, 1995). Nonneoplastic lesions have been observed in animals exposed to the more potent cPAHs, but only after exposure to levels well above those required to elicit a carcinogenic response. Benzo(a)pyrene has been demonstrated to induce adverse developmental and reproductive effects in experimental animals following oral exposure (ATSDR, 1995). These effects were manifested as reduced pup weights during postnatal development, sterility, reduced fertility, and an increased incidence of stillborns and resorptions (ATSDR, 1995). cPAHs are believed to induce tumors both at the site of application and systemically. Studies in laboratory animals have demonstrated that the cPAHs benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, chrysene, dibenz(a,h)anthracene and indeno(1,2,3-cd)pyrene have the ability to induce skin tumors following dermal exposure (ATSDR, 1995). Neal and Rigdon (1967) reported that oral administration of 250 ppm benzo(a)pyrene for approximately 110 days led to forestomach tumors in mice. Thyssen et al. (1981) observed respiratory tract tumors in hamsters exposed to up to 9.5 mg/m^3 benzo(a)pyrene for up to 96 weeks.

Benzo(a)pyrene, benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene, dibenz(a,h)anthracene, and indeno(1,2,3-cd)pyrene are classified by USEPA in Group B2—Probable Human Carcinogen (USEPA, 1998). USEPA has developed an oral slope factor of 7.3 $(mg/kg\text{-}day)^{-1}$ for benzo(a)pyrene based on the geometric mean of four slope factors calculated from three studies (Neal and Rigdon, 1967; Brune *et al*., 1981; Rabstein *et al*., 1973). Oral cancer slope factor for the other six cPAHs are derived by applying relative potency factors developed by USEPA (1993) to the oral slope factor for benzo(a)pyrene (benzo(a)anthracene, 0.73 $(mg/kg\text{-}day)^{-1}$; benzo(b)fluoranthene, 0.73 $(mg/kg\text{-}day)^{-1}$; benzo(k)fluoranthene, 0.073 $(mg/kg\text{-}day)^{-1}$; chrysene, 0.0073 $(mg/kg\text{-}day)^{-1}$; dibenz(a,h)anthracene, 7.3 $(mg/kg\text{-}day)^{-1}$; indeno(1,2,3-cd)pyrene, 0.73 $(mg/kg\text{-}day)^{-1}$).

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. *Toxicological profile for polycyclic aromatic hydrocarbons (PAHs).* August 1995.

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

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U.S. Environmental Protection Agency (USEPA). 1998. Integrated Risk Information System (IRIS). Environmental Criteria and Assessment Office. July 1998.

Acenaphthylene

Acenaphthylene is a member of the polycyclic aromatic hydrocarbons (PAH). PAHs are a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The data on acenaphthylene are limited.

No data were found regarding the pharmacokinetics, human toxicity or mammalian toxicity of acenaphthylene. Data from a single mutagenicity assay using acenaphthylene were positive (U.S. EPA, 1982).

U.S. Environmental Protection Agency (U.S. EPA) (1982) An exposure and risk assessment for polynuclear aromatic hydrocarbons (acenaphthylene). U.S. EPA Contract 68-01-6017. Office of Water Regulations and Standards. Washington, D.C.

Dibenzofuran

The general population is primarily exposed to dibenzofuran through inhalation of air which has been contaminated by a variety of combustion sources; dibenzofuran has been identified in tobacco smoke. Exposure may also occur through consumption of contaminated food and drinking water. Occupational exposure can occur through inhalation and dermal contact, particularly at sites engaged in combustion/carbonization processes such as coal tar and coal gasification operations. (SRC) Dibenzofuran has; a boiling point of 287 DEG C AT 760 MM HG, a melting point of 86-87 DEG C, a molecular weight of 168.19O, a log Kow of 4.12 (measured), measured water solubility of 10 ppm at 25 deg C., and a vapor pressure of 0.0044 mm Hg at 25 deg C.

No data were found regarding the pharmacokinetics of dibenzofuran.

The workplace air in a carbon-paste plant in Norway was found to contain a dibenzofuran particulate conc. of 0.7-1.8 ug/cu m(Bjoerseth et al., 1977). Monitoring of the workplace air in an aluminum reduction plant in Norway found gas-phase dibenzofuran levels of 0.44-61.0 ug/cu m and particulate phase levels of 0.02-0.14 ug/cu m(Bjoerseth et al., 1978).

Cumulative oral doses of 100 ug/kg are estimated to be the minimum toxic dose. Dermal exposure to soil concentrations of greater than 100 ppm are likely to produce chloracne.

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Acenaphthene

Acenaphthene is a member of the polycyclic aromatic hydrocarbons (PAH). PAHs are a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The database for acenaphthene is very limited.

No data were found regarding the pharmacokinetics of acenaphthene.

No data were found regarding the human toxicology of acenaphthene.

Adverse effects on the lungs, glands, and blood were observed in rats following aerosol administration of 12 mg/m^3 acenaphthene for 5 months (U.S. EPA, 1981).

Mutagenicity tests for acenaphthene were negative (U.S. EPA, 1981). Carcinogenicity tests were negative (IARC, 1983).

International Agency for Research on Cancer (IARC) (1983) *Monograph on the evaluation of carcinogenic risk of chemicals to man: polynuclear aromatic hydrocarbons*. 32:33-43.

U.S. Environmental Protection Agency (U.S. EPA) (1981) An exposure and risk assessment for acenaphthylene. U.S. EPA Contract No. 68-01-6017. Office of Water Regulations and Standards, Washington, D.C.

Anthracene

Anthracene is a polycyclic aromatic hydrocarbon (PAH). PAHs are a class of compounds which are non-polar and contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. As a PAH, anthracene is found in tobacco smoke, certain foods, and the emissions from industrial or natural burning.

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

Anthracene is a skin irritant and allergen (Sax, 1984). Humans exposed to anthracene in an occupational setting may demonstrate skin disorders (Clement, 1985). Anthracene has been associated with gastrointestinal tract toxicity in humans (Badiali et al, 1985). However, the usefulness of this study is limited due to confounding factors. Hematopoietic toxicity has also been observed in cancer patients who have been treated with anthracene-containing chemotherapeutics (Falkson et al, 1985). No control groups and concomitant exposure to other ingredients in the therapeutic agents prevents any definitive conclusions.

A subchronic study where anthracene was administered to mice by gavage for at least 90 days found no treatment-related effects at doses up to 1000 mg/kg-day (US EPA, 1989). The data on the carcinogenicity of anthracene are considered inadequate by EPA.

Tests for DNA damage, mutation, chromosome effects and cell transformation in a variety of eukaryotic cell preparations have shown negative results. The majority of tests using anthracene in prokaryotes are negative, but positive results are reported in one or two tests (ATSDR, 2002).

Agency for Toxic Substances and Disease Registry (ATSDR) (2002) Toxicological summary for polycyclic aromatic hydrocarbons. U.S. Public Health Service.

Badiali, D. et al. (1985) *Melanosis of the rectum in patients with constant constipation*. Dis Colon Rectum 28:241-245.

Clement (1985) Chemical, physical and biological properties of compounds present at hazardous waste sites.

Falkson, G. Klein, B., Falkson, H. (1985) *Hematological toxicity: experience with antracyclines adn anthracenes*. Exp. Hematol 13:64-71.

International Agency for Research on Cancer (IARC) (1983) *Monograph on the evaluation of carcinogenic risk of chemicals to man, anthracene*. 32:433-440.

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

Fluorene

Fluorene is a member of the polyaromatic hydrocarbons (PAH). PAHs constitute a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The data on fluorene are very limited. Low levels of (5 to 67 ug/kg) have been detected in smoked meats (U.S. EPA, 1982).

No data were found regarding the pharmacokinetics of fluorene.

The database for the toxicological effects of fluoranthene on humans, separate from other PAHs, is limited. Toxic effects attributable to mixtures of PAHs include a variety of skin lesions and non-cancer lung diseases such as bronchitis (IARC, 1973).

Limited information is available on the threshold effects of fluorene. An EPA study (EPA, 1989) indicated that CD-1 mice exposed by gavage to up to 500 mg/kg-day of fluorene showed hypoactivity as well as a decrease in red blood cell count and packed cell volume and hemoglobin. Increases in absolute and relative liver, spleen and kidney weights was also observed. Gershbein (1975) reported that partially hepatectomized rats fed a diet of 180 mg/kg-day of fluorene for 10 days showed a statistically significant increase in liver regeneration, which is indicative of the ability to induce a proliferative response. Fluorene is not reported to be a complete skin carcinogen (ATSDR, 2002). It was inactive as a tumor initiator when an estimated total dose of 1.0 mg was applied prior to the application of tetradecanoyl phorbol acetate (LaVoie et al, 1980).

There is no evidence that fluorene is genotoxic, but genotoxicity has been studied only in a few in vitro assays (ATSDR, 2002).

Agency for Toxic Substances and Disease Registry (ATSDR) (2002) Toxicological profile for polycyclic aromatic hydrocarbons. U. S. Public Health Service.

Gershbein, L.L. (1975) *Liver regeneration as influenced by the structure of aromatic and heterocyclic compounds*. Res Commun Chem Pathol Pharmacol 11:445-466.

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LaVoie, E.J. (1980) *Identification of mutagenic hydrodiols as metabolites of benzo(j)fluoranthene and bnezo(k)fluoranthene*. Cancer Research 40:4528-4532.

U.S. Environmental Protection Agency (U.S. EPA) (1982) An exposure and risk assessment of polycyclic aromatic hydrocarbons (fluorene). U.S. EPA Contract 68-01-6017. Office of Water Regulations and Standards, Washington, D.C.

U.S. Environmental Protection Agency (EPA) (1989) Mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, Ltd. Muskegon, MI for the Office of Solid Waste, Washington, D.C.

PESTICIDES AND POLYCHLORINATED BIPHENYLS

Alpha-Chlordane

Chlordane is a manmade pesticide used in the United States from 1948 to 1988. It was used to treat field crops and as a soil treatment to kill termites. Chlordane is not water soluble, and in soil, adsorbs strongly to the upper layers of soil especially heavy clayey soils and organic soils. Breakdown is slow; most is lost by evaporation in the first two to three days after application. However, chlordane can persist up to 20 years (ATSDR, 1994).

The effects observed in humans and animals exposed to chlordane do not appear to be route dependent. Absorption occurs readily by any route of exposure. Gastrointestinal symptoms are an early and consistent observation in acute human oral and inhalation exposure (Curley and Garrettson, 1969; Dadey and Kramer, 1953; USEPA, 1980; Olanoff *et al*., 1983). Chlordane causes neurological effects in humans following acute or prolonged oral, inhalation, or dermal exposures. Neurological effects, such as headache, dizziness, irritability, muscle tremors, confusion, convulsions, and coma are the first signs reported. Central nervous system effects have been reported in children following oral exposure (Aldrich and Holmes, 1969). Jaundice has been reported by persons lining in homes treated with chlordane (USEPA, 1980). Subtle serum enzyme level changes were observed in pesticide application workers in Japan (Ogata and Izushi, 1991). Acute oral and parenteral studies of animals exposed to low levels of chlordane are reported to show enzyme induction, minor histochemical and histomorphological changes, and liver hypertrophy within hours of exposure (Casterline and Williams, 1971; Cram *et al*., 1956; Den Tonkelaar and Van Esch, 1974; Hart *et al*., 1963; Johnson *et al*., 1986; Truhaut *et al*., 1974, 1975).

Chlordane is classified as Group B2 - Probable Human Carcinogen based on inadequate evidence of carcinogenicity from human studies and sufficient evidence of carcinogenicity from animal studies (USEPA, 1998). USEPA developed an oral cancer slope factor of $3.5x10^{-1}(mg/kg\text{-}day)^{-1}$ based on the geometric mean of five data sets of hepatocellular carcinomas in mice. USEPA developed a chronic oral RfD of $5x10^{-4}$ mg/kg-day based on several 24-month studies in which hepatic necrosis was seen in mice fed 5 ppm (0.75 mg/kg-day) and not in those fed 1 ppm (0.15 mg/kg-day) (Khasawinah and Grutsch, 1989). An uncertainty factor of 300 was used to derive the RfD.

Agency for Toxic Substances and Disease Registry (ATSDR). 1994. *Toxicological profile for chlordane*. May 1994.

Aldrich, F.D. and J.H. Holmes. 1969. Acute chlordane intoxication in a child: Case report with toxicological data. *Environ. Health* 19:129-132.

Casterline, J.L. and C.H. Williams. 1971. The effects of 28-day pesticide feeding on serum and tissue enzyme activities of rats fed diets of varying casein content. *Toxicol. Appl. Pharmacol*. 18:607-618.

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U.S. Environmental Protection Agency (USEPA). 1998. Integrated Risk Information System (IRIS). Environmental Criteria and Assessment Office. July 1998.

U.S. Environmental Protection Agency (USEPA). 1980. *Summary of Reported Pesticide Incidents Involving Chlordane*. Pesticide Incident Monitoring System Report No. 360. Office of Pesticide Programs.

Gamma-Chlordane

Chlordane is a manmade pesticide used in the United States from 1948 to 1988. It was used to treat

field crops and as a soil treatment to kill termites. Chlordane is not water soluble, and in soil, adsorbs strongly to the upper layers of soil especially heavy clayey soils and organic soils. Breakdown is slow; most is lost by evaporation in the first two to three days after application. However, chlordane can persist up to 20 years (ATSDR, 1994).

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Dieldrin

Dieldrin is a chlorinated cyclodiene insecticide that is structurally related to aldrin. Both aldrin and dieldrin are well absorbed through the lungs, skin, and gastrointestinal tract (Shell, 1984; Heath and Vanderkar, 1964; Hunter and Robinson, 1967, 1969; Sundaram *et al*., 1978a,b; Iatropoulous *et al*., 1975). Aldrin is metabolically converted to dieldrin in fatty tissues (ACGIH, 1986) and both are considered to have similar chemical and toxic effects (USEPA, 1988). Several human and animal studies have shown that adipose tissue is the primary storage depot for dieldrin, followed by the liver, brain, and whole blood (ATSDR, 1993). Acute symptoms of dieldrin intoxication in humans

and animals following ingestion or inhalation indicate CNS stimulation manifested primarily as irritability, salivation, tremors, and convulsions. Experimental studies indicate that dogs exposed for longer periods of time to levels as low as 1 mg/kg developed hepatic and renal toxicity (Fitzhugh *et al*., 1964; Treon and Cleveland, 1955; Walker *et al*., 1969). Rats fed dieldrin for 2 years developed hepatic lesions and nephritis at doses of 0.5 and 50 ppm, respectively (Fitzhugh *et al*., 1964). Dieldrin produced fetotoxic and/or teratogenic effects in hamsters fed a single oral dose of 50 mg/kg (approximately 84 ppm) and in mice fed a single oral dose of 25 mg/kg (approximately 6 ppm) (Ottolenghi *et al*., 1974). Dieldrin produced marked effects on fertility, gestation, viability, and lactation in mice given 25 mg/kg-day in a six-generation study (Deichmann, 1972). Dieldrin produces chromosomal aberrations in mouse, rat, and human cells and unscheduled DNA synthesis in rats and humans (Probst *et al*., 1981). Chronic oral exposure to dieldrin has produced an increase in hepatocellular tumors in mice (Davis, 1965; Epstein, 1975; NCI, 1978). In contrast, chronic feeding studies with dieldrin in rats indicate that exposure was associated with nonneoplastic changes in the liver (NCI, 1978; Fitzhugh *et al*., 1964). Ingestion of dieldrin by laboratory animals results in a decreased immune response (Loose 1982; Loose *et al*., 1981).

USEPA (1998) classified dieldrin as group B2 - Probable Human Carcinogen and developed an oral cancer slope factor of 1.6 10^{+1} $(mg/kg\text{-}day)^{-1}$ based on the increased incidence of liver carcinoma observed in male and female C3H mice (Davis, 1965; Epstein, 1975) and in male B6C3F1 mice (NCI, 1978). USEPA (1998) derived a chronic oral RfD for dieldrin of 5 10^{-5} mg/kg-day based on a study in which rats were fed dieldrin for 2 years and displayed liver lesions at dose levels of 0.005 mg/kg-day (1 ppm) and greater (Walker *et al*., 1969). An uncertainty factor of 100 was used to calculate the chronic RfD.

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Heptachlor Epoxide

Heptachlor epoxide is a contaminant and metabolite of the insecticide, heptachlor. Heptachlor is readily absorbed from the gastrointestinal tract following oral exposure (ATSDR, 1993). Acute symptoms due to heptachlor exposure in humans include irritability, excessive salivation, labored respiration, muscle tremors, and convulsions (USEPA, 1987). Acute exposure of animals to heptachlor and heptachlor epoxide produced tremors, convulsions, paralysis, and hypothermia (USEPA, 1985). Chronic exposure of experimental animals to dietary concentrations of heptachlor or heptachlor epoxide has been associated with increased liver weight and hepatocellular carcinoma; heptachlor also induced hepatic lesions (USEPA, 1987; Velsicol, 1955; Dow Chemical, 1955; Davis, 1965; Epstein, 1976; NCI, 1977; Velsicol, 1973). In the presence of metabolic activation, both heptachlor and heptachlor epoxide induced unscheduled DNA synthesis in transformed human

fibroblasts (Ahmed *et al*., 1977). Heptachlor also increased the frequency of chromosomal aberrations in bone marrow cells of mice (Markarjan, 1966). Results of studies with rodents also indicate that heptachlor epoxide induces reproductive and developmental effects (USEPA, 1987).

Heptachlor epoxide is classified as Group B2 - Probable Human Carcinogens (USEPA, 1998) based on sufficient evidence of carcinogenicity in animal studies and inadequate evidence of carcinogenicity in humans. Using the geometric mean of potency factors from four separate experiments in which mice exposed to dietary concentrations of heptachlor epoxide exhibited hepatocellular carcinomas (Davis, 1965; NCI, 1977; Velsicol, 1973), USEPA (1998) estimated an oral cancer slope factor for heptachlor epoxide of 9.1 $(mg/kg\text{-}day)^{-1}$. An oral RfD, based on chronic systemic toxicity, has also been calculated for heptachlor epoxide (USEPA, 1998). In a Dow Chemical study (1958), beagle dogs of both sexes fed heptachlor epoxide in their diet for 60 weeks developed increased liver-to-body weight ratios. No NOEL was determined from this study, but a LOEL of 0.5 ppm (0.0125 mg/kg-day) was identified from the available data. An oral RfD of $1.3\ \ 10^{-5}$ mg/kg-day for heptachlor epoxide was estimated from these data by applying an uncertainty factor of 1,000 to the LOEL (USEPA, 1998).

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4,4'-DDT, 4,4'-DDE, 4,4'-DDD

DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane) was a chemical widely used to control insects on agricultural crops and insects that carry diseases like malaria and typhus. Technical grade DDT is a mixture of three forms, 4,4'-DDT (85%), 2,4'-DDT (15%), and 2,2'-DDT (trace amounts) (ATSDR, 1994). All of these are white, crystalline, tasteless, and almost odorless solids. Also, DDE (1,1-dichloro-2,2- bis(p -chlorophenyl)ethylene) and DDD (1,1-dichloro-2,2- bis(p -chlorophenyl)ethane) sometimes contaminate technical grade DDT. DDD was also used to kill pests; one form of DDD (2,4'-DDD) has been used medically to treat cancer of the adrenal gland (ATSDR, 1994). DDT is no longer used as a pesticide in the United States except in cases of public health emergency. The most prevalent isomers for DDT, DDE, or DDD in the environment are the 4,4'-isomers (ATSDR, 1994).

DDT is absorbed by humans and experimental animals from the gastrointestinal tract (USEPA, 1984, 1980). Jenson et al. (1957) reported that 95% of ingested DDT in rats is absorbed from the gastrointestinal tract. Absorption of DDT through the skin is minimal (USEPA, 1980). In humans, DDT and its metabolites, DDD and DDE, are stored primarily in adipose tissue; storage of DDT in human tissues can last up to 20 years (NIOSH, 1978). Acute oral exposure to DDT in humans and animals may cause dizziness, confusion, tremors, convulsions, and paresthesia of the extremities. Allergic reactions in humans following dermal exposure to DDT have also been reported (USEPA, 1980). Long-term occupational exposure to DDT results in increased activity in hepatic microsomal enzymes, increased serum concentrations of enzymes and cholesterol, decreased serum concentrations of creatinine phosphokinase, increased blood pressure, and increased frequency of miscarriages (NIOSH, 1978). Blood, kidney, liver and neurological effects, immunosuppression, reduced fertility, embryotoxicity, and fetotoxicity have also been reported in animals following subchronic and chronic exposure to DDT (ATSDR, 1994; Laug *et al*., 1950; NIOSH, 1978; McLachlan and Dixon, 1972; Schmidt, 1973). For example, monkeys subchronically exposed to 50 mg/kg-day DDT exhibited loss of equilibrium and rats chronically exposed to 16 mg/kg-day DDT exhibited tremors by week 26 (ATSDR, 1994). In addition, rats exposed, in a two-generation feeding study, to 0.35 mg/kg-day DDT had decreased fertility (Green, 1969). DDT has been shown to be carcinogenic in mice and rats at several dose levels or dosage regimens. The principal site of action is the liver, but an increased incidence of tumors of the lung and lymphatic system have also been reported in several investigations (NIOSH, 1978; Tomatis *et al*., 1974; NCI, 1978).

4,4'-DDT, 4,4'-DDD, and 4,4'-DDE are classified by USEPA in Group B2 - Probable Human Carcinogen based on inadequate evidence of carcinogenicity from human studies and sufficient

evidence of carcinogenicity from animal studies (USEPA, 1998). For 4,4'-DDT, USEPA (1998) developed an oral cancer slope factor of 3.4 10^{-1} $(mg/kg\text{-}day)^{-1}$ based on the geometric mean of a number of carcinogenicity studies. USEPA (1998) developed an oral cancer slope factor for 4,4'-DDD of 2.4 10^{-1} $(mg/kg\text{-}day)^{-1}$ based on an increased incidence of lung tumors in male and female mice, liver tumors in male mice, and thyroid tumors in male and female rats. USEPA (1998) developed an oral cancer slope factor for 4,4'-DDE of $3.4x10^{-1}$ $(mg/kg\text{-}day)^{-1}$ based on an increased incidence of liver tumors in two strains of mice and hamsters, and thyroid tumors in male and female rats by diet. In addition, USEPA (1998) developed a chronic oral RfD for 4,4'-DDT of 5 10^{-4} mg/kg-day based on a study in which liver lesions were observed in rats fed 5 ppm but not in those fed 1 ppm (0.05 mg/kg-day) DDT for 27 weeks (Laug et al., 1950). An uncertainty factor of 100 was used to derive the RfD.

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Polychlorinated Biphenyls (PCBs)

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

PCBs in pure form are readily and extensively absorbed through the gastrointestinal tract and somewhat less readily through the skin; PCBs are presumably readily absorbed from the lungs, but few data are available that experimentally define the extent of absorption after inhalation (USEPA, 1985). Studies have found oral absorption efficiency on the order of 75% to>90% in rats, monkeys and ferrets (Albro and Fishbein, 1972; Allen *et al*., 1974; Tanabe *et al*., 1981; Bleavens *et al*., 1984; Clevenger *et al*., 1989). PCBs distribute preferentially to adipose tissue and concentrate in human breast milk due to its high fat content (ATSDR, 1991). The binding of PCBs to a soil or sediment matrix inhibits absorption by all routes (ATSDR, 1995).

Dermatitis and chloracne (a disfiguring and long-term skin disease) have been the most prominent and consistent findings in studies of occupational exposure to PCBs. Several studies examining liver function in exposed humans have reported disturbances in blood levels of liver enzymes. Reduced birth weights, slow weight gain, reduced gestational ages, and behavioral deficits in infants were reported in a study of women who had consumed PCB-contaminated fish from Lake Michigan (USEPA, 1985). Reproductive, developmental, hepatic, immunotoxic, and immunosuppressive effects appear to be the most sensitive end points of PCB toxicity in nonrodent species, and the liver appears to be the most sensitive target organ for toxicity in rodents (USEPA, 1985). For example, adult monkeys exposed to dietary concentrations of 0.028 mg/kg-day Aroclor-1016 for approximately 22 months showed no evidence of overt toxicity; however, the offspring of these monkeys exhibited decreased birth weight and possible neurological impairment (Barsotti and Van Miller, 1984; Levin *et al*., 1988; Schantz *et al*., 1989, 1991).

A number of studies have suggested that PCB mixtures are capable of increasing the frequency of tumors including liver tumors in animals exposed to the mixtures for long periods (Kimbrough *et al*., 1975; NCI, 1978; Schaeffer *et al*., 1984; Norback and Weltman, 1985). In addition, studies have suggested that PCB mixtures can act to promote or inhibit the action of other carcinogens in rats and

mice (USEPA, 1985). It is known that PCB congeners vary greatly in their potency in producing biological effects, such as cancer; however, USEPA (1998) generally considers Aroclor-1260 to be the Aroclor with the greatest tumorigenic potential and, therefore, conservatively uses this Aroclor to be representative of all PCB mixtures for the evaluation of carcinogenic effects. Nevertheless, USEPA (1998) has acknowledged that there is some evidence that mixtures containing highly chlorinated biphenyls are more potent inducers of hepatocellular carcinoma in rats than are mixtures containing less chlorine by weight following oral exposure (USEPA, 1998). The responses are mostly limited to the livers in rats and mice, although there is a suggestion that some PCB mixtures may also affect the stomach of rats and monkeys (Chase *et al*., 1989). Statistically significant increases in malignant tumors have not been observed in animal studies with PCB mixture containing less than 60 percent chlorine content (Chase *et al*., 1989). There is some suggestive evidence that Aroclor-1254 induces hepatocellular adenomas and carcinomas combined in male rats based on the reclassification and reevaluation of the NCI (1978) tumor data conducted by Ward (1985). However, the majority of tumors were benign (statistically significant alone), while the few malignant tumors (carcinomas) were not statistically elevated by themselves. At present, there is uncertainty as to whether or not Aroclor-1248, -1242, or -1232 are tumorigenic in animals. This is because there are no valid cancer bioassays for these mixtures (Chase *et al*., 1989).

Existing epidemiological data do not indicate a consistent tumorigenic effect among individuals exposed to PCBs. ATSDR (1995) concluded that occupational studies involving predominantly inhalation and dermal exposures to PCBs have suggested an association between the development of liver, gastrointestinal, hematopoietic and skin cancer and PCB exposure. However, the majority of these studies were mortality studies that reported nonstatistically significant results, were confounded by concurrent exposure to other chemicals (many of which are considered to be potential carcinogens), had small sample sizes or number of deaths, or unquantified PCBs exposures. In addition, there is no consistent pattern of associations among the various studies, either with respect to type of human cancers observed or the nature and extent of PCB exposures.

USEPA (1998) classifies PCBs as Group B2 - Probable Human Carcinogens based on sufficient evidence in animal bioassays and inadequate evidence from studies in humans. USEPA (1998) recently revised the oral slope factor for PCBs to multiple possible slope factors corresponding to three different tiers. The appropriate tier for used depends on the level of risk and likely persistence of the congeners evaluated. The top tier, for "high risk and persistence," is considered most appropriate at this site. The criteria for use of this tier, suggested by USEPA (1998), are as follows: (1) food chain exposures; (2) sediment or soil ingestion; (3) dust or aerosol inhalation; (4) dermal exposure, if an absorption factor has been applied; (5) presence of dioxin-like, tumor-promoting, or persistent congeners; and (6) early-life exposures. The upper-bound slope factor, to be used for RME risk estimates, is 2.0 $(mg/kg\text{-}day)^{-1}$ and the central-estimate slope factor, for central tendency risk estimates, is 1.0 $(mg/kg\text{-}day)^{-1}$. Dose-response data were generated based on the incidence of liver hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas in female Sprague-Dawley rats exposed to Aroclor-1260, -1254, -1242, and -1016 separately in one study (Brunner *et al*., 1996) and only Aroclor-1260 in another study (Norback and Weltman, 1985). USEPA (1998) derived an oral RfD of 2 10^{-5} mg/kg-day for Aroclor-1254 based on a 55-month oral study conducted in monkeys (Arnold *et al*., 1993a,b; Tryphonas *et al*., 1989, 1991a,b). A

LOAEL of 0.005 mg/kg-day was observed, and significant effects were observed including immunological system effects, ocular exudate, inflamed Meibomian glands, and distorted growth of finger and toe nails. An uncertainty factor of 300 was used to calculate the RfD.

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PESTICIDES AND POLYCHLORINATED BIPHENYLS – DIOXIN

Dioxins

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

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

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

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

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

TCDD is not directly genotoxic, but the TCDD-Ah receptor complex can bind to specific DNA enhancer sequences. This induces a pleiotropic sequence of genetic expression whose products may

activate pro-mutagens. The US EPA has been re-evaluating the health effects of dioxins for the past several years and is expected to issue a final report in 1995. This report is expected to conclude that TCDD is a probable human carcinogen for soft tissue sarcomas and is a likely human reproductive hazard.

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INORGANICS

Antimony

Antimony is a metal which occurs both in the trivalent and pentavalent oxidation states (USEPA, 1980). Absorption of this metal via oral routes of exposure is low (10% for antimony, tartrate; 1% for all other forms) (ATSDR, 1990). Organic antimony is more toxic than the inorganic compounds due to increased absorption. Humans and animals exposed acutely by oral or inhalation exposures to either the trivalent or pentavalent forms of antimony displayed electrocardiogram (ECG) changes and myocardial lesions (USEPA, 1980). Pneumoconiosis has been observed in humans exposed by acute inhalation and dermatitis has occurred in individuals exposed either orally or dermally. Following acute oral exposure to antimony trioxide or potassium antimony tartrate, both humans and laboratory animals (dogs) manifested nausea and vomiting (ATSDR, 1990). Humans and laboratory animals (i.e., rat and pig) chronically exposed to antimony compounds (antimony trioxide, pentoxide, and trisulfide) via inhalation manifested respiratory effects including macrophage proliferation, fibrosis and pneumonia at LOAELs ranging from 0.046 to 86.3 mg/m^3 (ATSDR, 1990). Chronic oral exposure in rats (0.35 mg/kg-day) resulted in altered blood glucose and blood cholesterol levels and decreased lifespan (Schroeder *et al*., 1970). A single report (Balyeava, 1967) noted an increase in spontaneous abortions, premature births, and gynecological problems in 318 female workers exposed to a mixture of antimony metal, antimony trioxide, and antimony pentasulfide dusts. No change in the incidence of cancer was observed in laboratory animals (i.e., rats, mice) fed 0.262 or 0.35 mg/kg-day antimony as potassium antimony tartrate for a lifetime.

USEPA (1998) derived a chronic oral RfD of 4 10^{-4} mg/kg-day for antimony (as potassium antimony tartrate) based on a chronic oral study (Schroeder *et al*., 1970) in which rats given the metal in drinking water had altered blood glucose and blood cholesterol levels and decreased lifespan. An uncertainty factor of 1,000 and a LOAEL of 0.35 mg/kg-day were used to derive the oral RfD.

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Arsenic

Arsenic is difficult to characterize as a single analyte because it has complex chemistry. It may be trivalent or pentavalent and is widely distributed in nature (ATSDR, 1993). Both inorganic and organic forms of arsenic are readily absorbed via oral and inhalation routes. Soluble forms are more readily absorbed than insoluble forms (USEPA, 1984). Approximately 95% of soluble inorganic arsenic administered to rats is absorbed from the gastrointestinal tract (Coulson *et al*., 1935; Ray-Bettley and O'Shea, 1975). Approximately 70–80% of arsenic deposited in the respiratory tract of humans has been shown to be absorbed (Holland *et al*., 1959). Dermal absorption is not significant (USEPA, 1984). At mining sites, arsenic is expected to occur in naturally occurring mineral assemblages with considerably lower bioavailability than expected in soluble inorganic arsenic salts (Davis *et al*., 1992).

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

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

USEPA classified arsenic as Group A - Human Carcinogen (USEPA, 1998). USEPA (1998) derived an oral cancer slope factor of 1.5 $(mg/kg\text{-}day)^{-1}$ based on two epidemiological studies (Tseng *et al*., 1968; Tseng, 1977) which indicated an increased incidence of skin cancer in individuals exposed to arsenic in drinking water. A chronic oral RfD of 3 10^{-4} mg/kg-day was calculated for arsenic based on incidence of keratosis and hyperpigmentation in humans (Tseng, 1977). An uncertainty factor of 3 and a modifying factor of 1 were used to derive the chronic oral RfD. Applying USEPA's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of

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Barium

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

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

Subchronic and chronic oral or inhalation exposure primarily affects the cardiovascular system resulting in elevated blood pressure. A lowest-observed-adverse-effect level (LOAEL) of 0.51 mg barium/kg/day based on increased blood pressure was observed in chronic oral rat studies (Perry et al. 1983), whereas human studies identified a no-observed-adverse-effect level (NOAEL) of 0.21 mg barium/kg/day (Wones et al. 1990, Brenniman and Levy 1984). The human data were used by the EPA to calculate a chronic and subchronic oral reference dose (RfD) of 0.07 mg/kg/day. In the Wones et al. study, human volunteers were given barium up to 10 mg/L in drinking water for 10 weeks. No clinically significant effects were observed. An epidemiological study was conducted by Brenniman and Levy in which human populations ingesting 2 to 10 mg/L of barium in drinking water were compared to a population ingesting 0 to 0.2 mg/L. No significant individual differences were seen; however, a significantly higher mortality rate from all combined cardiovascular diseases was observed with the higher barium level in the 65+ age group. The average barium concentration was 7.3 mg/L, which corresponds to a dose of 0.20 mg/kg/day. Confidence in the oral RfD is rated medium by the EPA.

Subchronic and chronic inhalation exposure of human populations to barium-containing dust can result in a benign pneumoconiosis called “baritosis.” This condition is often accompanied by an elevated blood pressure but does not result in a change in pulmonary function. Exposure to an air concentration of 5.2 mg barium carbonate/m^3 for 4 hours/day for 6 months has been reported to result in elevated blood pressure and decreased body weight gain in rats (Tarasenko et al. 1977). Reproduction and developmental effects were also observed. Increased fetal mortality was seen after untreated females were mated with males exposed to 5.2 mg/m^3 of barium carbonate. Similar results

were obtained with female rats treated with 13.4 mg barium carbonate/m^3. The NOAEL for developmental effects was 1.15 mg/m^3 (equivalent to 0.8 mg barium/m^3). An inhalation reference concentration (RfC) of 0.005 mg/m^3 for subchronic and 0.0005 mg/m^3 for chronic exposure was calculated by the EPA based on the NOAEL for developmental effects. These effects have not been substantiated in humans or other animal systems.

Barium has not been evaluated by the EPA for evidence of human carcinogenic potential

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Cadmium

Gastrointestinal absorption of cadmium in humans ranges from 5 to 6% (USEPA, 1985a). Based on a comprehensive model for inhaled cadmium, the deposition rate of particulate airborne cadmium is 5–50% (i.e., 5% of particles greater than 10 microns and up to 50% of particles less than 0.1 microns), and 50–100% of the cadmium deposited was absorbed (Nordberg *et al*., 1985). Cadmium bioaccumulates in humans, particularly in the kidney and liver (USEPA, 1985a,b). Acute oral exposure to cadmium in laboratory animals resulted in systemic, immunological, neurological, developmental, and reproductive effects at doses of 2–138 mg/kg-day (ATSDR, 1993). Chronic oral or inhalation exposure of humans to cadmium has been associated with renal dysfunction, itai-itai disease (bone damage), hypertension, anemia, endocrine alterations, and immunosuppression. Renal toxicity occurs in humans chronically exposed to cadmium in food at LOAEL of 0.0075 mg/kg-day. In laboratory animals (i.e., rat, mouse) chronic oral exposure to cadmium results in increased blood pressure, hematological, and renal effects at LOAELs ranging from 0.014 to 57 mg/kg-day (ATSDR, 1993). Teratogenic and reproductive effects (i.e., deceased fetal and birth weight, delayed ossification, behavioral impairment, and reduced fertility) were reported in laboratory animals (i.e., rat, mice, dogs) subchronically exposed to cadmium in drinking water at LOAELs ranging from 0.04 to 40 mg/kg-day (ATSDR, 1993). Epidemiological studies have demonstrated a strong association between inhalation exposure to cadmium and cancers of the lung, kidney, and prostate (USEPA, 1985b; Thun *et al*., 1985). In experimental animals, cadmium induces injection-site sarcomas and testicular tumors. When administered by inhalation, cadmium chloride is a potent pulmonary

carcinogen in rats. Cadmium is a well-documented animal teratogen (USEPA, 1985b).

USEPA (1998) classified cadmium as Group B1 - Probable Human Carcinogen by inhalation. This classification applies to agents for which there is limited evidence of carcinogenicity in humans from epidemiologic studies. Using renal toxicity as an endpoint, and a safety factor of 10, USEPA (1998) derived two separate oral RfDs. The RfD associated with oral exposure to drinking water is 5 10^{-4} mg/kg-day, and is based on the LOAEL of 0.005 mg/kg in humans (USEPA, 1985a; Friberg *et al*., 1974). The RfD associated with exposure to cadmium in food is 1 10^{-3} mg/kg-day.

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Chromium

Chromium exists in two states, as chromium (III) and as chromium (VI). Following oral exposure, absorption of chromium (III) has been reported to be 0.4% while absorption of chromium (VI) has been observed to be as high as 10% (ATSDR, 1993). However, chromium (VI) is rapidly reduced to chromium (III) after penetration of biological membranes and in the gastric environment (ATSDR, 1993). Chromium is an essential micronutrient and is not toxic in trace quantities (USEPA, 1980).

Alterations in liver enzyme activities were noted in rats administered an oral dose of 13.5 mg/kg-day chromium (VI) for 20 days (Kumar *et al*., 1985). Rats subchronically administered higher concentrations of chromium VI (98 mg/kg-day) have exhibited adverse effects on renal function

(Diaz-Mayans *et al*., 1986). No significant changes, however, were detected in the livers or kidneys of rats exposed to 2.7 mg/kg-day or 3.5 mg/kg-day chromium (III) or chromium (VI), respectively, in the drinking water for 1 year (MacKenzie *et al*., 1958; ATSDR, 1993). CNS effects including hypoactivity have been reported in rats when exposed to subchronic levels of 98 mg/kg-day chromium VI in drinking water (Diaz-Mayans *et al*., 1986).

Workers exposed to 2 $\mu g/m^3$ chromic acid vapors (mean duration of 2.5 years), a soluble chromium (VI) compound, exhibited atrophy and ulceration of the nasal mucosa and transient decrease in lung function (Lindberg and Hedenstierna, 1983). There is, however, insufficient scientific evidence that chromium (III) compounds by themselves elicit atrophy of the nasal mucosa or adverse respiratory effects in humans (ATSDR, 1993). Furthermore, epidemiological studies of worker populations have clearly established that inhaled chromium (VI) is a human carcinogen; the respiratory passages and the lungs are the target organs (Mancuso, 1975; USEPA, 1984).

Inhalation of chromium (III) or ingestion of chromium (VI) or (III) has not been associated with carcinogenicity in humans or experimental animals (USEPA, 1984). Oral exposure of pregnant mice (gestational days, 1 to 19) to 57 mg/kg-day chromium (VI) resulted in embryolethal effects (e.g., increased resorptions and postimplantation loss), reduced ossification and gross anomalies (Trivedi et al., 1989). Chromium (III) does not appear to cause fetotoxic or teratogenic effects in rats (ATSDR, 1993). Reproductive effects in the form of decreased sperm count were noted in mice administered oral doses of 4.6 mg/kg-day chromium (VI) (225 ppm) and 3.5 mg/kg-day chromium (III) (172 ppm) for 7 weeks (Zahid *et al*., 1990).

USEPA (1998) classified inhaled chromium (VI) in Group A—Human Carcinogen by the inhalation route. Inhaled chromium (III) and ingested chromium (III) and (VI) have not been classified with respect to carcinogenicity (USEPA, 1998). USEPA (1998) derived a chronic oral RfD of 5 10^{-3} mg/kg-day for chromium (VI) based on a study by MacKenzie et al. (1958) in which no adverse effects were observed in rats exposed to 2.4 mg chromium (VI)/kg-day in drinking water for 1 year. A safety factor of 500 was used to derive the RfD. USEPA (1998) developed an oral RfD of 1 mg/kg-day for chromium (III) based on a study in which rats were exposed to chromic oxide baked in bread. No effects due to chromic oxide treatment were observed at any dose level (Ivankovic and Preussman, 1975); however, hepatotoxicity was the effect of concern. An uncertainty factor of 1,000 was used to calculate the RfD.

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Copper

Copper is a reddish metal that occurs naturally in rock, soil, water, sediment, and air. Its average concentration in the earth's crust is about 50 parts copper per million parts soil. Copper also occurs naturally in plants and animals. It is an essential element for all known living organisms including humans and other animals.

Chromosomal aberrations were induced in isolated rat hepatocytes when incubated with copper sulfate (Sina et al., 1983). Casto et al. (1979) showed enhanced cell transformation in Syrian hamster embryo cells infected with simian adeno virus with the addition of cuprous sulfide and copper sulfate. High concentrations of copper compounds have been reported to induce mitosis in rat ascites cells and recessive lethals in Drosophila melanogaster. Law (1938) reported increases in the percent lethals observed in Drosophila larvae and eggs when exposed to copper by microinjection (0.1% copper sulfate) or immersion (concentrated aqueous copper sulfate), respectively.

Hematological effects in workers employed in a copper processing factory have been reported by

Finelli et al. (1981). However, interpretation of the study results is limited by the finding of elevated iron, lead, and cadmium in hair samples of exposed workers.

Metal fume fever, has been reported in factory workers exposed to copper dust or fumes (Armstrong et al. 1983; Gleason 1968; Stokinger 1981).

Moriya et al. (1983) reported no increase in mutations in E. coli and S. typhimurium strains TA98, TA1535, TA1537 and TA1538 incubated with up to 5 mg copper quinolinolate/plate and in S. typhimurium TA98 and TA100 incubated with up to 5 mg copper sulfate/plate.

Demerec et al. (1951) reported dose-related mutagenic effects in E. coli with 2 to 10 ppm copper sulfate in a reverse mutation assay. Negative results were obtained with copper sulfate or copper chloride in assays using S. cerevisiae (Singh, 1983) and Bacillus subtilis (Nishioka, 1975, Matsui, 1980, Kanematsu et al., 1980). Errors in DNA synthesis from poly(c)templates have been induced in viruses incubated with copper chloride or copper acetate (Sirover and Loeb, 1976).

Bionetics Research Labs (1968) studied the carcinogenicity of a copper-containing compound, copper hydroxyquinoline, in two strains of mice (B6C3F1 and B6AKF1). Groups of 18 male and 18 female 7-day-old mice were administered 1000 mg copper hydroxyquinoline/kg bw (180.6 mg Cu/kg) suspended in 0.5% gelatin daily until they were 28 days old, after which they were administered 2800 ppm (505.6 ppm Cu) in the feed for 50 additional weeks. No statistically significant increases in tumor incidence were observed in the treated 78-week-old animals. In the same study, Bionetics Research Labs (1968) administered a single subcutaneous injection of gelatin (control) or 1000 mg of copper hydroxyquinoline/kg bw (180.6 mg Cu/kg) suspended in 0.5% gelatin to groups of 28-day-old mice of both strains. After 50 days of observation, the male B6C3F1 had an increased incidence of reticulum cell sarcomas compared with controls. No tumors were observed in the treated male B6AKF1 mice, and a low incidence of reticulum cell sarcomas was observed in the treated female mice of both strains.

Gilman (1962) administered intramuscular injections containing 20 mg of cupric oxide (16 mg Cu), cupric sulfide (13.3 mg Cu), and cuprous sulfide (16 mg Cu) into the left and right thighs of 2- to 3-month-old Wistar rats. After 20 months of observations, no injection-site tumors were observed in any animals, but other tumors were observed at very low incidence in the animals receiving cupric sulfide (2/30) and cuprous sulfide (1/30). As the relevance of the organic copper compound to the observation of sarcoma induction is uncertain and the incidence of tumors in rats treated i.m. with inorganic copper was very low, data are considered inadequate for classification.

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Cyanide

Both cyanide gases and salts are used in industrial processes. Minor uses of HCN include insecticides and rodenticides for fumigating enclosed spaces (e.g., grain storage area). Cyanide salts

are used mainly in the electroplating and metal-finishing industries. Minor applications of the salts include the manufacture of dyes and pigments, as well as use as insecticides and rodenticides (ATSDR, 1997).

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

The fatal effects of exposure to high doses of cyanide over short periods of time are well known. Inhalation of 100 ppm HCN for 0.5 to 1 hour has been fatal to humans. Exposure to HCN vapors resulted in palpitations, shortness of breath, pain over the heart, vertigo, and involuntary eye movements (Carmelo, 1955), cyanosis, headache, altered EEG, and left-sided blindness (Sandberg, 1967). The cardiovascular effects are believed to be secondary to the CNS effects (ATSDR, 1997). HCN fumigators also exposed by inhalation and dermal contact developed palpitations, shortness of breath, pain over the heart, vertigo, and involuntary eye movements (Carmelo, 1955). The LD_{50} in humans for ingestion exposure has been reported to be 1.5 mg/kg/day of CN-. A lower fatal dose in humans has been reported at 0.6 mg/kg/day CN- (ATSDR, 1997). Brief exposure to lower levels of cyanide has resulted in rapid, deep breathing, shortness of breath, convulsions, and loss of consciousness. Because cyanide is not sequestered in the body, these effects are reversible over time. However, longer-term exposure to these low levels has resulted in CNS, thyroid gland, and cardiovascular effects. Several occupational studies of workers exposed to HCN produced thyroid abnormalities. In a case-control study of electroplating workers exposed to 6.4 to 10.4 ppm HCN for 5 to 15 years, 56 percent of the exposed group had enlarged thyroid glands and significantly elevated hemoglobin levels and lymphocyte counts. It should be noted that these workers were also exposed to volatiles, there were varying exposure levels, and unmatched controls (El Ghawabi et al., 1975). Workers in a silver-reclaiming factory exposed an average of 10.5 months to a TWA of 16.6 mg/m^3 HCN developed headache, dizziness, and mild thyroid abnormalities (Blanc et al., 1985). No studies of developmental effects in humans resulting from inhalation of cyanide are available.

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

Male rats were fed 30 mg/kg/day cyanide for 11.5 months and developed vacuolization and myelin degeneration of the spinal cord (Philbrick et al., 1979). No CNS effects were reported by Howard

and Hanzell (1955) for rats fed up to 10.8 mg/kg/day of CN-in HCN-fumigated feed for two years. Dogs fed 0.27 and 0.53 mg/kg/day cyanide in capsules for 16 weeks developed degenerative changes in the CNS ganglion cells, reduced ribonucleic acid (RNA) content, and inflammation (Hertting et al., 1960). Numerous studies of orally exposed pregnant animals have found maternal toxicities and developmental abnormalities in the offspring. Pregnant hamsters exposed to cyanide as D,L-amygdalin (a component of laetrile) exhibited maternal toxicity at 250 mg/kg and greater. Fetuses were examined at 15-days gestation, and dose-related abnormalities were observed in this group (Willhite, 1982). Female rats were fed a basal cassava diet containing 12 mg/kg HCN and a basal diet with 1.25 gm KCN per kg diet prior to mating, during gestation, and through lactation. The weanlings were subsequently fed these same diets. Those weanlings exposed to higher levels of cyanide in utero and during the post-weaning period had significantly decreased protein-efficiency ratios. Both the dams and weanlings fed the potassium cyanide enhanced diet had significantly increased serum thiocyanate levels (Tewe and Maner, 1981).

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

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Lead

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

Lead can be absorbed by the oral, inhalation or dermal exposure routes (see section on Relative Absorption Factors). Gastrointestinal absorption of lead varies considerably depending upon chemical form, dietary intake, and age (Forbes and Reina, 1974; Barltrop and Meek, 1975). The deposition and absorption of inhaled lead depends upon particle size, chemical form and the rate and depth of breathing (Randall et al., 1975; Nozaki, 1966; Chamberlain et al., 1975). Once absorbed, lead is distributed to the various organs of the body, with most distribution occurring into mineralized tissues (ATSDR, 1990). Placental transfer to the developing fetus is possible (Bellinger et al., 1987). Inorganic lead is not known to be biotransformed within the body. Absorbed lead is excreted via the urinary or fecal routes (ATSDR, 1990)

Cases of acute lead poisoning in humans are not common and have not been studied in experimental animals as thoroughly as chronic lead poisoning. Symptoms of acute lead poisoning from deliberate ingestion by humans may include vomiting, abdominal pain, hemolysis, liver damage, and reversible tubular necrosis (USEPA, 1984). Subacute exposures in humans reportedly may produce a variety of neurological effects including dullness, restlessness, irritability, poor attention span, headaches,

muscular tremor, hallucinations, and loss of memory. Nortier et al., (1980) report encephalopathy and renal damage to be the most serious complications of chronic toxicity in man and the hematopoietic system to be the most sensitive. For this reason, most data on the effects of lead exposure in humans are based upon blood lead levels. The effects of lead on the formation of hemoglobin and other hemoproteins, causing decreased levels, are reportedly detectable at lower levels of lead exposure than in any other organ system (Betts et al., 1973). Peripheral nerve dysfunction is observed in adults at levels of 30 to 50 mg/dL-blood. Children's nervous systems are reported to be affected at levels of 15 mg/dL-blood and higher (Benignus et al., 1981). In high doses, lead compounds may potentially cause abortions, premature delivery, and early membrane rupture (Rom, 1976).

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

Results of *in vitro* studies with human lymphocyte cultures using lead acetate were nearly equally positive and negative. Results of in vivo tests are also contradictory but suggest that lead may have an effect on chromosomes (sister chromatid exchange). Results for gene mutations, DNA modification, and recombinations in various microorganisms using lead acetate, lead nitrate and lead chloride were consistently negative with or without metabolic activation. Lead chloride has been reported to inhibit both DNA and RNA synthesis. In *in vitro* mammalian test systems, lead acetate gave conflicting results.

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

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Manganese

Manganese is considered to be among the least toxic of the trace metals and, in fact, is considered to be an essential element (NRC, 1989). The oral absorption of dietary manganese ranges from 3 to 10% (USEPA, 1998). However, manganese is absorbed to a greater extent following inhalation exposures. The National Research Council has established a provisional recommended dietary allowance for adults of 2 to 5 mg/day (NRC, 1989). The effects following acute exposure to manganese are unknown. Chronic occupational exposure to manganese dust (0.02–2.6 mg/m^3) has been associated with respiratory symptoms and pneumonitis (Chandra *et al*., 1981) and higher levels have been associated with a condition known as manganism, a progressive neurological disease characterized by speech disturbances, tremors, and difficulties in walking. For example, male workers exposed to manganese dioxide, tetroxide and various salts (TWA of total airborne manganese dust ranged from 0.07 to 8.61 mg/m^3) experienced an increased incidence of psychomotor disturbances (e.g., reaction time, hand-eye coordination and hand steadiness) (Roels *et al*., 1987). Other effects observed in humans occupationally exposed to manganese dust include hematological (Chandra *et al*., 1981; Flinn *et al*., 1941; Kesic and Hausler, 1954), cardiovascular (Saric and Hrustic, 1975) and reproductive effects (Cook *et al*., 1974; Emara *et al*., 1971; Lauwerys *et al*., 1985; Rodier, 1955). In adults, a safe intake of manganese from dietary sources ranges from 2 to 10 mg/day (10 mg/day = 0.14 mg/kg-day) (WHO, 1973; NRC, 1989; Schroeder *et al*., 1966). Individuals who chronically ingested drinking water from natural wells containing manganese

concentrations of 1,600–2,300 µg/L (0.06 mg/kg-day), showed a statistically significant increase in minor neurologic effects (neurologic exam scores) (Kondakis *et al*., 1989). The dietary intake of manganese was unaccounted for in this study, and therefore, USEPA withdrew its previous assessment that used this study to determine a quantitative dose-response relationship for manganese in drinking water. Higher concentrations in drinking water (0.8 mg/kg-day) have resulted in symptoms including lethargy, increased muscle tonus, tremor and mental disturbances (Kawamura *et al*., 1941). Chronic oral exposure of rats to manganese chloride can also result in CNS dysfunction (Leung *et al*., 1981; Lai *et al*., 1982). Chronic inhalation exposure of experimental animals (monkeys, rats, mice, hamsters) has resulted in respiratory effects; however, other studies have demonstrated that these effects may be immunological in origin (ATSDR, 1992). Manganese has not been reported to be teratogenic; however, this metal has been observed to cause depressed reproductive performance and reduced fertility in humans and experimental animals (USEPA, 1984a). Certain manganese compounds have been shown to be mutagenic in a variety of bacterial tests. Manganese chloride and potassium permanganate can cause chromosomal aberrations in mouse mammary carcinoma cells. Manganese was moderately effective in enhancing viral transformation of Syrian hamster embryo cells (USEPA, 1984a,b).

USEPA (1998) established a weight-of-evidence classification for manganese of D (not classifiable as to human carcinogenicity). USEPA (1998) derived an oral RfD of 1.4 10^{-1} mg/kg-day for total oral manganese ingestion based on a NOAEL of 0.14 mg/kg-day (10 mg/day) in humans chronically exposed to dietary levels (WHO, 1973; Schroeder *et al*., 1966; NRC, 1989). The organ of concern was the CNS, and an uncertainty factor of one was used to derive the RfD. USEPA (1998) recommends a modifying factor of 3 to assess exposures from drinking water; therefore, an oral RfD of 2.4 10^{-2} mg/kg-day for drinking water has been derived.

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36.

Mercury

In humans, inorganic mercury is absorbed following inhalation and oral exposure; however, only 7–15% of administered inorganic mercury is absorbed following oral exposure (USEPA, 1984; Rahola *et al*., 1971; Task Group on Metal Accumulation, 1973; ATSDR, 1993). Organic mercury is almost completely absorbed from the gastrointestinal tract and is assumed to be well absorbed via inhalation in humans (USEPA, 1984). A primary target organ for inorganic compounds is the kidney. Acute and chronic exposures of humans to inorganic mercury compounds have been associated with anuria, polyuria, proteinuria, and renal lesions (Goyer, 1996). Chronic occupational exposure of workers to elemental mercury vapors (0.026–0.2 mg/m^3) has been associated with mental disturbances, tremors, and gingivitis (USEPA, 1984; ATSDR, 1993). Animals exposed to inorganic mercury for 12 weeks have exhibited proteinuria, nephrotic syndrome and renal disease (Druet *et al*., 1978). Rats chronically administered inorganic mercury (as mercuric acetate) in their diet for 2 years exhibited a dose-related increase in glomerular nephritis at concentrations as low as 1.27 mg/kg-day (Fitzhugh *et al*., 1950). The CNS is a major target for organic mercury compounds. Adverse effects in humans, resulting from subchronic and chronic oral exposures to organic mercury compounds, have included destruction of cortical cerebral neurons, damage to Purkinje cells, and lesions of the cerebellum. Clinical symptoms following exposure to organic mercury compounds have included paresthesia, loss of sensation in extremities, ataxia, and hearing and visual impairment (WHO, 1976; ATSDR, 1993). Adverse kidney effects are also prominent in animals following chronic ingestion of organic mercury (0.5 ppm phenyl mercuric acetate or 0.015 mg Hg/kg-day) (Fitzhugh *et al*., 1950). Embryotoxic and teratogenic effects, including malformations of the skeletal and genitourinary systems, have been observed in animals exposed orally to organic mercury (USEPA, 1984). Both organic and inorganic compounds are reported to be genotoxic in eukaryotic systems (Leonard *et al*., 1984). Elevated incidence of fetal resorption was observed in hamsters exposed to 31.4 mg/kg-day inorganic mercury (Gale, 1974). There is evidence to suggest methylmercury chloride induces renal tumors, mostly adenocarcinomas in two strains of male mice (ICR and B6C3F1) (Hirano *et al*., 1986; Mitsumori *et al*., 1981, 1990). However, monkeys, cats and rats chronically administered methyl mercury in the diet did not develop an elevated tumor incidence (Ikeda *et al*., 1973; Charbonneau *et al*., 1976; Vershuuren *et al*., 1976). Furthermore, elevated cancer incidence has not been reported in humans who ingested methylmercury-contaminated fish in the Minamata area of Japan (Katsuna, 1968) or in humans who ingested methylmercury fungicide-treated grains in Iraq and were followed for 13 years (Greenwood, 1985).

USEPA (1998) reported an oral RfD for chronic exposures of 3 10^{-4} mg/kg-day for inorganic mercury based on the formation of mercury-induced autoimmune glomerulonephritis found in several oral and parenteral studies conducted in the Brown Norway rat studies (Druet *et al*., 1978; Bernaudin *et al*., 1981; Andres, 1984). An uncertainty factor of 1,000 was used to derive the RfD. An oral RfD of 1 10^{-4} mg/kg-day for methylmercury (organic) has been reported by USEPA (1998) based on several studies reporting human poisonings in particular fetal methylmercury poisoning in the relationship of maternal hair and child effects (Marsh *et al*., 1987). An uncertainty factor of 10 was used to derive the RfD for methyl mercury.

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Nickel

Nickel in the ambient atmosphere typically exists as a constituent of suspended particulate matter (U.S. EPA, 1985). The greatest volume of nickel emitted into the atmosphere is the result of fossil fuel combustion. Other sources of nickel emissions are primary production, incinerators, metallurgy, chemical manufacturing, cement manufacturing, coke ovens, nickel recovery, asbestos mining/milling and cooling towers.

Studies of nickel absorption have shown that it is absorbed by all routes of exposure to varying degrees, primarily dependent on the chemical form (see section on Relative Absorption Factors). Absorbed nickel is bound to serum components and distributed to body organs, reaching highest concentrations in kidney and lung tissue (Whanger, 1973). Nickel is not known to be biotransformed. Excretion of absorbed nickel is primarily through urine, with minor excretory routes through hair and sweat (ATSDR, 1988).

Nickel carbonyl $Ni(CO)_4$ is a particularly toxic form of nickel upon inhalation and causes chest pain, dry coughing, hyperpnea, cyanosis, occasional gastrointestinal symptoms, sweating, visual

disturbances and severe weakness. This is often followed by pulmonary hemorrhage, edema and cellular derangement. Survivors may be left with pulmonary fibrosis. In the workplace, nickel dermatitis may result at high nickel concentrations. At lower concentrations some susceptible individuals develop eczema-like lesions. The threshold for these health effects is much greater than exposures which occur in the ambient environment. The major adverse effects of nickel in man are dermatitis, chemical pneumonitis, and lung and nasal cancers.

Deaths occurred in rats and mice at concentrations greater than 3.3 and 1.7 mg/m^3 nickel, respectively, upon extended inhalation exposure to $NiSO_4$ (Dunnick et al., 1987). Mice exposed to Ni_3S_2 died due to necrotizing pneumonia at 7.3 mg/m^3 nickel (Benson et al., 1987). Prolonged exposure of hamsters to nickel oxide at 41.7 mg/m^3 resulted in decreased survival due to emphysema (Wehner et al., 1975). Oral LD_{50}s in rats vary depending upon the nickel-containing compound to which the rats were exposed. These range from 355 mg compound/kg (118 mg Ni/kg) for nickel acetate (Haro, 1968) to greater than 5000 mg compound/kg for nickel oxide, nickel sulfide, and nickel subsulfide (Mastromatteo, 1986). Rats fed diets containing nickel sulfate hexahydrate at 0, 250, 500 and 1000 ppm nickel showed no adverse effects over three generations in fertility, gestation, viability or lactation.

Weak evidence exists for the mutagenicity of nickel in bacterial and mammalian cells. Nickel appears to induce chromosomal aberrations in cultured mammalian cells (Larramendy et al., 1981), but not in vivo (Waksvik and Boysen, 1982). Occupational studies of human exposure indicate that certain nickel compounds appear to be carcinogenic via inhalation. However, there is no evidence of carcinogenicity in mammals through ingestion or dermal exposure (U.S. EPA, 1985). Nickel subsulfide has been found to be carcinogenic via the inhalation route in rats (Ottolenghi et al., 1974). Studies on nickel exposure via the oral route are inadequate to reach conclusions on carcinogenicity (ATSDR, 1988).

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Selenium

Sodium selenate is among the most mobile form of selenium because of its high solubility and inability to adsorb to soil particles. Bioavailability of selenium is dependent upon the ambient conditions, which determine the form of selenium present (ATSDR, 1994).

Human and animal data suggest that many chemical forms of selenium produce similar effects. Selenium is known to be an essential micronutrient for humans and animals; therefore, inadequate as well as excessive selenium intake can cause negative health effects (ATSDR, 1994). One proposed mechanism of intermediate and chronic toxicity for selenium compounds is that under conditions of excess body levels of selenium, selenium atoms begin to replace the sulfur atoms in structural and enzymatic proteins (Shamberger, 1970), destroying the protein structural and functional integrity. This mechanism of action is unlikely to be organ specific; therefore, under this proposed mechanism, toxic levels of selenium would be expected to affect multiple organ systems. Furthermore, differential sensitivities of the various organ systems to selenium exposure would be expected on the basis of differential accumulation or retention of selenium compounds (Goyer, 1996).

The primary target organ in humans and in animals upon acute exposure to high concentrations of selenium by inhalation or oral routes is the lung, with cardiovascular, hepatic, and renal systems also affected. Lesser effects are observed in all other organ systems except the musculoskeletal system. The liver is the primary target organ for the oral toxicity of sodium selenite, sodium selenate, and organic forms of selenium in animals following intermediate and chronic exposure. In humans, liver cirrhosis or dysfunction are the result of chronic selenosis (ATSDR, 1994). Endocrine effects were found following intermediate oral exposure. Following chronic oral exposure to selenium

compounds, the primary effects in humans are dermal and neurological. As evidenced by populations in China, chronic exposure to high selenium levels in the diet can cause diseased nails and skin as well as hair loss. Higher levels can cause neurological problems including unsteady gait and paralysis. However, studies of populations living in areas of naturally occuring high selenium concentrations in the United States have not revealed adverse health effects in those populations (Yang *et al*., 1989a,b). Following intermediate and chronic oral exposure to selenium compounds, the primary effects in livestock exposed to naturally occuring selenium in range plants are also dermal and neurological. Studies in animals with high selenium concentrations demonstrate that many organ systems retain selenium and are affected. The primary effects in laboratory animals exposed to inorganic selenium salts or to selenium-containing amino acids are cardiovascular, gastrointestinal, hematological, hepatic, dermal, immunological, neurological, and reproductive (ATSDR, 1994). Selenium is a teratogen in birds. However, studies of Chinese populations and laboratory animals have not found evidence of teratogenic effects in mammals (ATSDR, 1994).

USEPA (1998) has determined that selenium is not classifiable as to human carcingenicity (Class D). USEPA (1998) derived an oral RfD for selenium and compounds of 5 10^{-3} mg/kg-day based on human epidemiological studies of a population in China with unusually high environmental concentrations of selenium in the soil and food supply; dermal effects (nail disease) in humans indicative of chronic selenosis (Yang *et al*., 1989a,b) were exhibited. An uncertainty factor of 3 was used to derive the chronic RfD.

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Thallium

Thallium and its salts are readily and rapidly absorbed through the skin, lungs, and mucous membranes of the mouth and gastrointestinal tract (ATSDR, 1992). Percutaneous absorption has also been reported to occur through rubber gloves (Rumack, 1986). Thallium is acutely toxic to humans regardless of the chemical form of the compound or route of administration. Hundreds of cases of thallotoxicosis due to ingestion of thallium-based pesticides have been reported (ACGIH, 1986). Children poisoned by thallium ingestion have exhibited neurological abnormalities including mental retardation and psychoses (ACGIH, 1986). The effects of thallium toxicity are similar in humans and animals. The most commonly noted response to thallium exposure is alopecia, but neurological and gastrointestinal findings are frequently found. Such effects include ataxia, lethargy, painful extremities, peripheral neuropathies, convulsions, endocrine disorders, psychoses, nausea, vomiting, and abdominal pains (Bank, 1980). It has been noted that the degree and duration of exposure to thallium and its salts can influence the clinical picture of thallium intoxication. Subchronic feeding studies conducted with rats observed marked growth depression and a nearly complete loss of hair (USEPA, 1986; Clayton and Clayton, 1981). Exposure to thallium salts during critical developmental stages in chicks and rats has been reported to be associated with the induction of adverse developmental outcomes (Karnofsky *et al*., 1950). Pre- and postnatally exposed rat pups have exhibited hydronephrosis, fetal weight reduction and growth retardation (Clayton and Clayton, 1981; Gibson and Becker, 1970). Thallium has also been shown to cross the placenta and, presumably, enter the fetal blood system (Clayton and Clayton, 1981). Thallium has not been demonstrated to be carcinogenic in humans or experimental animals and may have some antitumor activity (Clayton and Clayton, 1981).

USEPA (1998) derived oral RfDs for certain thallium salts (i.e., thallium acetate, thallium carbonate, thallium chloride, thallium nitrate, thallium selenite and thallium sulfate) of between 8-9 10^{-5} mg/kg-day based on the same 90-day subchronic rat study (USEPA, 1986; MRI, 1986). For this risk assessment, an oral RfD of 8 10^{-5} mg/kg-day for thallium salts is used to assess all thallium exposures. The same endpoints of toxicity were observed and an uncertainty factor of 3,000 was used to derive the chronic RfD.

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Vanadium

The absorption of vanadium through the gastrointestinal tract of animals is low (2.6% for vanadium pentoxide in rats) (Conklin *et al*., 1982). Soluble vanadium compounds that are inhaled and deposited are readily absorbed (50–100%) (ATSDR, 1992). Because vanadium has low solubility, its absorption through skin is thought to be quite low, although no specific studies were located regarding dermal absorption (ATSDR, 1992). Pentavalent vanadium compounds are generally considered to be more toxic than other valence states. Many incidents of short-term and long-term occupational exposures to vanadium, mainly vanadium pentoxide dust, have been reported. Inhalation causes respiratory tract irritation, coughing, wheezing, labored breathing, bronchitis, chest pains, eye and skin irritation and discoloration of the tongue (NIOSH, 1977; NAS, 1974). Humans subchronically exposed to vanadium pentoxide (0.1 mg/m^3) via inhalation experienced respiratory irritation (Zenz and Berg, 1967). Experimental animals (i.e., rats, monkeys) subchronically exposed to vanadium compounds (vanadium pentoxide, bismuth orthovanadate) manifested alveolar proteinosis and increased pulmonary resistance at concentrations of 2.5–4.7 mg/m^3 (Lee and Gillies, 1986; Knecht *et al*., 1985). Effects seen in experimental animals following chronic inhalation exposure include fatty degeneration of the liver and kidneys, hemorrhage, and bone marrow changes (Browning, 1969). Humans subchronically exposed to ammonium vanadyl tartrate (1.3 mg/kg-day) via capsules did not manifest any adverse effects (Dimond *et al*., 1963). However, experimental animals (i.e., rats, mice) orally exposed to vanadium compounds (sodium metavanadate, sodium orthovanadate, ammonium metavanadate) exhibited mild systemic effects (decreased weight gain, vascular infiltration, spleen hypertrophy and increased ventricular pressure) at doses as low as 0.57 mg/kg-day (ATSDR, 1992). Rats chronically administered 0.77 mg/kg-day (5 ppm) vanadium in their drinking water showed no adverse effects (Schroeder *et al*., 1970). Pre- and postnatally exposed rat pups have exhibited reduced pup weight and length and facial hemorrhage (ATSDR, 1992). Vanadium has not been demonstrated to be carcinogenic in humans or experimental animals.

USEPA (1997) reports a chronic oral RfD of 7 10^{-3} mg/kg-day based on a chronic study in which

rats received vanadium in their drinking water (Schroeder *et al*., 1970). A NOAEL of 0.77 mg/kg-day (5 ppm) and an uncertainty factor of 100 were used to develop the RfD.

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VPH/EPH

C_9 – C_{10} Aromatics; C_{11} – C_{22} Aromatics

The toxicity for the $C_9 – C_{10}$ and $C_{11} – C_{22}$ aromatic fractions is based upon exposure studies to mixtures of compounds within the entire range of C_9 through C_{32} aromatic hydrocarbon compounds (MADEP, 2003). Alkenes with the same carbon range were also evaluated similarly to aromatics in this fraction (MADEP, 1994). The TPHCWG identified 77 individual compounds within the C_9 - C_{16} carbon range, of which only 8 (acenaphthene, biphenyl, fluorene, anthracene, fluoranthene, naphthalene, and pyrene) have available USEPA derived oral RfDs. For the $C_{17} – C_{35}$ range, there are no previously identified RfDs for this carbon range. The TPHCWG identified pyrene (C_{16}) as a conservative surrogate because for this fraction because it has a lower carbon number than any of the compounds in this fraction. The RfD for pyrene is 0.03 mg/kg-d (TPHCWG, 1997).

The oral RfDs for the C_9 – C_{16} range from 0.03 to 3 mg/kg/day. An RfD for a naphthalenes/methylnaphthalene mixture was calculated as 0.03 mg/kg/day based upon target organ toxicity in the liver, thyroid and bladder. Rats were dosed orally with 0, 300, 600, or 1000 mg/kg for 13 weeks (unpublished data). Mean body weights and food consumption were significantly decreased in male rats at 1000 mg/kg. Histopathologic changes were centrilobular hepatocellular hypertrophy in both sexes at *all* dose levels; hyperplasia and hypertrophy of the thyroid in both sexes at *all* dose levels; and hyperplasia of the urinary bladder in male rats at *all* dose levels and in female rats at 300 mg/kg. An uncertainty factor of 10,000 (10 most sensitive, 10 animal to human, 10 subchronic to chronic, 10 LOAEL to NOAEL) was applied to the LOAEL of 300 mg/kg to arrive at the RfD of 0.03 mg/kg-d (TPHCWG, 1997). This value is consistent with the oral RfD for pyrene of 0.03 mg/kg-d, which is based upon kidney toxicity observed in a subchronic mouse study (IRIS, 2003). MA DEP recommends that an RfD of 0.03 mg/kg/day for the aromatic hydrocarbons containing 9 through 32 carbons continue to be used to represent the toxicities of all compounds in this fraction (MADEP 2002a).

Of the 77 compounds identified in the C_9 - C_{32} aromatic hydrocarbon range, a US EPA derived RfC was identified for isopropylbenzene (C_9) (0.4 mg/m^3), commonly known as cumene (US EPA, 1997a) and for naphthalene (C_{10}) (0.003 mg/m^3) (IRIS, 2003). In addition, recent inhalation studies on the trimethylbenzenes have been identified. The RfC for isopropylbenzene is based upon two subchronic inhalation studies in mice. The critical treatment-related effects were increased relative and absolute kidney weights in female rats, and increased relative and absolute adrenal weights in both sexes at the highest concentrations (5909 mg/m^3) tested. A NOAEL of 492 mg/m^3 was used to derive the RfC of 0.4 mg/m^3. The NOAEL was adjusted for continuous exposure and an uncertainty factor of 1000 (10 for subchronic to chronic extrapolation, 10 for animal to human extrapolation, 3 for sensitive individuals and 3 for database deficiency in reproductive effects) was applied to the NOAEL to derive the inhalation RfC (MADEP, 2002a). The RfC for naphthalene is based upon a chronic inhalation study in mice. The critical treatment-related effects were nasal effects such as hyperplasia and metaplasia in respiratory and olfactory epithelium, respectively were observed in both sexes at all doses tested. A LOAEL of 52 mg/m3 was converted to a human equivalent

concentration (HEC) of 9.3 mg/m^3 and an uncertainty factor of 3000 (10 to extrapolate from mice to humans, 10 to protect sensitive humans, 10 to extrapolate from a LOAEL to a NOAEL, and 3 for database deficiencies including the lack of a 2-generation reproductive toxicity study and chronic inhalation data for other animal species) to arrive at a chronic RfC for naphthalene of 0.003 mg/m^3.

In two subchronic inhalation studies in which rats were exposed to 1,2,4-trimethylbenzene (TMB) or 1,2,3-TMB, the treatment critical effect was demonstrated to be significant changes in CNS function (Gralewicz et al., 1997, Korsak and Rydzynski, 1996). For both studies the NOAEL was 123 mg/m^3. An RfC 0.02 mg/m^3 was derived from the identified NOAEL of 123 mg/m^3 by adjusting for continuous exposure and by applying an uncertainty factor of 1000 (10 for subchronic to chronic extrapolation, 10 for animal to human extrapolation, and 10 to account for sensitive individuals) (MADEP, 2002a).

Naphthenes are catalytically converted to aromatic compounds to make high-octane gasoline blending components. A portion of this wide-boiling range hydrocarbon stream can be separated by distillation and used for other purposes. One such distillate is a mixture containing primarily 9-carbon aromatic compounds usually consisting of isomers of ethyltoluene (28%) and trimethylbenzene (40 - 55%). Other C_9 minor components include isopropylbenzene (3%), n-propylbenzene (4%), and other aromatics containing more than 10 carbon atoms (6%). The percentages of the components may differ slightly from one distillate to another. These C_9 aromatic mixtures are commonly known as high flash aromatic naphtha (HFAN) and are used mainly as solvents (Douglas et al., 1993). Clark et. al. (1989) exposed male rats to high flash aromatic naphtha vapors at 0, 450, 900 or 1800 mg/m^3, 6 hours/day, 5 days/week for 12 months. Transient reduction in body weight gain was observed in male and female rats that did not last through the duration of the study. Hematological and clinical chemistry tests did not show any consistent dose-related effects. A possible increase in male "aggression" at the highest concentration was believed to be related to treatment. There was also a significant increase in male liver and kidney weights in the high exposure group. The TPHCWG (1997) determined 900 mg/m^3 as a NOAEL for hepatic effects in male rats. By adjusting the NOAEL for continuous exposure (NOAEL x 6/24 x 5/7) and by applying an uncertainty factor of 1000 (10 for animal to human extrapolation, 10 for human variability and 10 for subchronic to chronic extrapolation), an RfC of 0.2 mg/m^3 was estimated. The TPHCWG recommended that this RfC value (0.2 mg/m^3) be a surrogate for the entire C_9 - C_{16} fraction.

According to an evaluation of the database by the MADEP (2002a), the NOAEL of 900 mg/m^3 is higher than the NOAELs for other endpoints determined for the aromatic mixtures. The developmental and maternal NOAEL from the McKee et al. (1990) mouse study was 491 mg/m^3 and the developmental NOAEL from the Ungvary et al. (1983) rat study was 589 mg/m^3. No maternal NOAEL was identified in the Ungvary et al. study. The studies reviewed have demonstrated that pregnant animals are more sensitive than their non-pregnant counterparts and the male animals tested. In male rats, reduced weight gain was the only anomaly observed at the highest exposure concentration (7362 mg/m^3) (API, 1990), while this concentration was lethal to 22% of pregnant and non- pregnant female rats and 44% of pregnant female mice. A factor of 10 applied to the systemic NOAEL of 900 mg/m^3 to adjust for sensitive individuals may not be adequate to protect the most

sensitive species, the pregnant mother and the fetus. The total uncertainty factor applied by MA DEP to the TPHCWG derived RfC of 0.2 mg/m^3 would be 10 (3 to account for developmental effects and 3 to adjust for database deficiency. The deficiency is an absence of direct information on whether the data on C_9 aromatic mixtures are representative of all compounds in the C_9 - C_{16} aromatic group). The adjusted RfC is 0.02 (0.2/10) mg/m^3. Based on this information, MA DEP recommended an RfC value of 0.02 mg/m^3 as a surrogate toxicity number for the C_9 - C_{16} aromatic TPH fraction in its May 2002 Draft Updated Petroleum Hydrocarbon Fraction Toxicity Values For The VPH/EPH/APH Methodology document. However, in its October 2002 Final Characterizing Risks Posed by Petroleum Contaminated Sites: Implementation of the MADEP VPH/EPH Approach, the MADEP recommended RfC for the $C_9 – C_{10}$ and $C_{11} – C_{22}$ aromatic fractions is 0.05 mg/m^3. Personal communication with MADEP indicated that due to the new EPA RfC, naphthalene will be evaluated on its own and will not be considered as part of the derivation of the RfC for these carbon fractions, thus making the value slightly less conservative (MADEP, 2003).

The $C_9 – C_{10}$ and $C_{11} – C_{22}$ aromatic fractions are not considered carcinogenic. There are no oral slope factors or unit risk values for these fractions.

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C_{19} – C_{36} Aliphatic Fraction

The toxicity for the C_{19} – C_{36} aliphatic fraction is based upon exposure studies to white mineral oils representing different molecular weight (MW) fractions to derive their toxicity values. White mineral oils are a complex mixture of highly refined mineral hydrocarbons consisting primarily of saturated paraffinic hydrocarbons (predominantly branched chain alkanes) and naphthenic hydrocarbons (alkanes containing one or more saturated cyclic structures). These oils are pure aliphatic hydrocarbons with no aromatic components and other contaminants. They are approved by the US Food and Drug Administration as direct food additives and also used in cosmetics and pharmaceutical products (MA DEP, 2002a).

Target organ/effects for the C_{19} – C_{36} aliphatic fraction include liver and lymphatic tissue (Schuurman et al., 1994). The lower molecular weight (C_{17}-C_{34}) mineral oils demonstrated effects in the liver and mesenteric lymph nodes. Essentially no effects were observed with the higher molecular weight ($C_{>34}$) mineral oils at the highest dose tested. No other toxicity information was identified for these compounds

The RfD of 2 mg/kg/day derived by the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG) and recommended by MA DEP (2002b) is based upon the no-observed-adverse-effect level (NOAEL) of 200 mg/kg/d identified for the studies conducted by Shuurman et al. (1994).

No appropriate inhalation toxicity data were identified for individual components or fractions in C_{19}

- C_{36} aliphatic carbon range. This may be because hydrocarbon constituents in this fraction are not volatile and inhalation is not a likely exposure pathway. However, as in the high molecular weight aromatic hydrocarbons, aliphatic compounds in C_{17} - C_{32} carbon range can bind to soil particles. Inhalation exposure to respirable particulates containing high molecular weight PHCs is possible; but there are no data to estimate inhalation toxicity to particulate-bound hydrocarbons (MA DEP 2002a).

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C_9 – C_{18} Aliphatic Fraction

The toxicity for the C_9 – C_{18} aliphatic fraction is based upon exposure studies to mixtures of compounds within this hydrocarbon fraction of interest. The data on petroleum streams were given more weight for the derivation of toxicity criteria for the $C_{>8}$ - C_{16} fraction because of their low aromatic content (MA DEP, 2002a).

Target organs/effects for the C_9 – C_{18} aliphatic fraction include blood, serum chemistry, liver, kidney, and adrenals (Anon., 1991a; Anon., 1991b; Anon., 1990). The results of a study by Lund et al., (1995) demonstrated that 6 months of inhalation exposure to dearomatized white spirit (C_7 - C_{11}) induced long-lasting and possibly irreversible effects in the nervous system of the rat.

No developmental effects were detected in rats exposed to 0, 1742 or 5226 mg/m^3 of isoparaffinic hydrocarbon vapors during gestation day 6-15. The maternal and developmental NOAEL was 5226 mg/m^3. These data, however, were not published (TPHCWG, 1997). No other developmental/reproductive studies were identified.

The RfD of 0.1 mg/kg/day derived by the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG) and recommended by MA DEP (2002b) is based upon three studies with oral exposures to mixtures of compounds within the size range of carbon compounds of interest.

Based on the Lund et al. (1995) study, the MA DEP (2002b) derived an RfC of 0.2 mg/m^3 based on neurotoxicity.

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C_5 – C_8 Aliphatic Fraction

Based upon MADEP recommendation (MADEP, 2002a); n-hexane is the representative compound for the C_5 – C_8 aliphatic fraction, therefore this toxicity profile is based upon n-hexane. n-Hexane was originally selected by MA DEP as the indicator for this range because its toxicity has been well investigated and also because of some evidence demonstrating that the other alkanes in the group may exhibit similar neurotoxicity.

n-Hexane is a colorless liquid with a slightly disagreeable odor that is used in mixtures as an industrial solvent. Pure n-hexane is widely used in laboratories as an extractant for nonpolar compounds and for the calibration of instrumentation used in the analysis of volatile organic

compounds (VOCs) and total petroleum hydrocarbons (TPH). Liquid n-hexane volatilizes readily and has a very low solubility in water. Due to its ability to volatilize, the primary route of exposure to n-hexane is via inhalation. N-Hexane is readily absorbed from the lungs, however absorption from the gastrointestinal tract and the skin has not been well characterized. The primary site of metabolism is the liver. Excretion of n-hexane occurs via the lungs (10-20% total inhaled n-hexane is exhaled) and via the kidneys (2,5-hexanedione is the major metabolite recovered in urine) (ATSDR, 1999).

The primary target organ for n-hexane is the nervous system. Several epidemiological and animal studies have demonstrated that humans and animals exposed to n-hexane suffered from motor and sensory deficits that were associated with axonal degeneration in the peripheral nervous system. In many of the epidemiological studies, exposure was to mixtures containing commercial grade hexane or other aliphatic mixtures within the specified carbon ranges for this fraction. The mixtures contained n-hexane with levels ranging from 12.3 to 64%. Although none of the epidemiological studies permit the estimation of reference toxicity values because of data inadequacy (such as lack of control population and exact exposure estimation), they strongly suggest that commercial hexane or other mixtures within the group containing low levels of n-hexane may cause peripheral neurotoxicity (Yamada, 1972; Gaultier et al., 1973; Yamamura, 1969).

There are also some inhalation and oral animal studies on hexane mixtures that demonstrated peripheral neurotoxicity (Miyagaki, 1967; Krasavage et al., 1980)

Saturated hydrocarbons in the C_5 - C_8 fraction other than n-hexane and its isomers include n-pentane, n-heptane, n-octane and their structural (branched chain and cyclic) isomers. Unlike n-hexane, few human and animal toxicity studies are available on these compounds.

n-Hexane does not appear to effect other organ systems at doses lower than the concentrations that cause neurotoxic effects, nor does it appear to cause developmental effects in humans or animal models. Male rats exposed to n-hexane evidenced bilateral testicular damage (ATSDR, 1999).

An oral RfD of 0.04 mg/kg/day is recommended by the MA DEP (2002b) and is calculated from a lowest-observed-adverse-effect level (LOAEL) of 4000 mg/kg/day based on morphologic changes indicative of "giant axonal" neuropathy, which included multifocal axonal swellings, axonal myelin infolding and paranodal myelin retraction in rats dosed once daily, 5 days/week over a 90 - 120-day period (Krasavage et al., 1980).

Of the chemicals within this subgroup, inhalation toxicity values exist only for n-hexane (US EPA RfC of 0.2 mg/m^3 and ATSDR MRL of 2.0 mg/m^3). Adequate data were not identified to develop RfCs for any of the other individual compounds in this carbon range. The available data suggest there may be compounds in this hydrocarbon fraction in addition to n-hexane that may cause peripheral or central nervous system effects. However, the data do not permit estimation of toxicity values for the individual compounds or mixtures. MA DEP (2002b) recommends the use of US EPA's RfC of 0.2 mg/m^3.

n-Hexane has not been evaluated for carcinogenicity by the US EPA.

ATSDR 1999. Toxicological Profile for Hexane. Department of Health and Human Services, US Public Health Service, Agency for Toxic Substances and Disease Registry. Atlanta, GA. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp113.html

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Appendix C.10

Chemical Specific Permeability Coefficients

C.10 Chemical Specific Permeability Coefficients

CAS #	Chemical	Permeability Constant (cm/hr) Kp
ORGANIC COMPOUNDS		
208968	Acenaphthylene	9.11E-02
98862	Acetophenone	3.72E-03
71432	Benzene	1.49E-02
50328	Benzo-a-pyrene	7.01E-01
74839	Bromomethane	2.84E-03
108907	Chlorobenzene	2.82E-02
124481	Chlorodibromomethane	3.22E-03
75003	Chloroethane	6.07E-03
106445	Cresol, p-	7.66E-03
72548	DDD	1.79E-01
53703	Dibenzo(a,h)anthracene	1.51E+00
541731	Dichlorobenzene, 1,3-	5.79E-02
106467	Dichlorobenzene, 1,4-	4.20E-02
75343	Dichloroethane, 1,1-	6.74E-03
156592	Dichloroethene, cis-1,2-	1.10E-02
156605	Dichloroethene, trans-1,2-	1.10E-02
75354	Dichloroethylene, 1,1-	1.17E-02
60571	Dieldrin	1.22E-02
100414	Ethylbenzene	4.93E-02
1634044	Methyl tert-butyl ether	2.11E-03
75092	Methylene chloride	3.54E-03
91576	Methylnaphthalene, 2-	9.17E-02
91203	Naphthalene	4.66E-02
85018	Phenanthrene	1.44E-01
1746016	TCDD	8.07E-01
127184	Tetrachlorethylene	3.34E-02
108883	Toluene	3.11E-02
120821	Trichlorobenzene, 1,2,4-	6.63E-02
79005	Trichloroethane, 1,1,2-	6.44E-03
79016	Trichloroethylene	1.16E-02
75014	Vinyl chloride	5.60E-03
1330207	Xylenes (total)	4.71E-02
INORGANIC COMPOUNDS		
57125	Arsenic	1.00E-03
7440382	Chromium	1.00E-03
7440473	Lead	NA
7439965	Manganese	1.00E-03
7440020	Nickel	2.00E-04

Appendix C.11

Relative Bioavailability of Arsenic in Sediments from the Aberjona River

L2003-131 Mar 2004

RELATIVE BIOAVAILABILITY OF ARSENIC IN SEDIMENTS FROM THE ABERJONA RIVER

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ACKNOWLEDGEMENTS

The work described in this report is the product of a team effort involving a number of people. In particular, the authors would like to acknowledge the efforts and support of the following:

- Margaret E. Dunsmore, BS, helped with all aspects of animal handling and dosing, as well as urine collection and sample preparation.

- Dr. John Drexler at the University of Colorado, Boulder, performed the characterization of the sediment samples and test materials, including *in vitro* testing of bioaccessibility and electron microprobe and particle size analyses of the test materials.

- Dr. Edward Hinderberger of L.E.T., Inc., Columbia, Missouri, provided prompt and reliable chemical analysis of all of the samples for total arsenic concentrations.

EXECUTIVE SUMMARY

The gastrointestinal absorption of arsenic from two composite sediment samples collected from the banks of the Aberjona River was measured using young swine. Groups of animals (four animals per dose group) were given oral doses of a reference material (sodium arsenate) or site sediment twice a day for 12 days. Urine excreted by each animal was collected on days 6/7, 8/9 and 10/11. The urinary excretion fraction (UEF) (the ratio of the amount excreted per 48 hours divided by the dose given per 48 hours) was calculated for sodium arsenate and each test material using linear regression analysis. The relative bioavailability (RBA) of arsenic in a test material compared to that in sodium arsenate was calculated as:

$$RBA = \frac{UEF(test\ material)}{UEF(sodium\ arsenate)}$$

The results are summarized below:

Test Material	Description	Arsenic Conc. (ppm)	Relative Bioavailability	
			Best Est.	90% CI
TM1	Composite sample of three sediments with arsenic concentrations greater than 500 ppm	676	37%	32% – 41%
TM2	Composite sample of three sediments with arsenic concentrations of 180-460 ppm	313	51%	46% – 56%

These data indicate that arsenic in site sediments is absorbed less extensively than arsenic in drinking water. Use of these site-specific data is likely to improve the accuracy of risk estimates for humans who may be exposed to the sediments.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

RELATIVE BIOAVAILABILITY OF ARSENIC IN ABERJONA RIVER SEDIMENTS

1.0 INTRODUCTION

Accurate assessment of the health risks resulting from oral exposure to any chemical frequently requires knowledge of the amount of the chemical absorbed from the gastrointestinal tract into the body. This information on absorption may be described either in absolute or relative terms:

Absolute Bioavailability (ABA) is the ratio of the amount of chemical absorbed compared to the amount of chemical ingested:

$$ABA = \frac{Absorbed\ Dose}{Ingested\ Dose}$$

This ratio is also referred to as the oral absorption fraction (AF_0).

Relative Bioavailability (RBA) is the ratio of the absolute bioavailability of some test material compared to the absolute bioavailability of some appropriate reference material, usually the chemical dissolved in water or some fully soluble form that completely dissolves when ingested:

$$RBA = \frac{ABA\ (test\ material)}{ABA\ (reference\ material)}$$

For example, if 100 ug of arsenic dissolved in drinking water were ingested and a total of 90 ug entered the body, the ABA would be 0.90 (90%). Likewise, if 100 ug of arsenic contained in soil were ingested and 30 ug entered the body, the ABA for soil would be 0.30 (30%). If the arsenic dissolved in water was used as the reference substance for describing the relative amount of arsenic absorbed from soil, the RBA would be 0.30/0.90 = 0.33 (33%).

Using Relative Bioavailability Data to Improve Risk Calculations for Arsenic

When reliable data are available on the relative bioavailability of arsenic in a site medium (e.g., soil, sediment), this information can be used to improve the accuracy of exposure and risk calculations for that medium at that site as follows:

$$RfD(adjusted) = \frac{RfD\ (IRIS)}{RBA}$$

$$SF(adjusted) = SF(IRIS) \cdot RBA$$

Alternatively, it is also acceptable to adjust the dose (rather than the toxicity factors) as follows:

$$Dose(adjusted) = Dose(default) \cdot RBA$$

This adjustment in dose is mathematically equivalent to adjusting the toxicity factors as described above.

Purpose of This Study

USEPA Region 1 is currently investigating potential human health risks from arsenic in sediment samples from along the Aberjona River and associated wetlands and floodplain areas. This study was performed to obtain site-specific data on the relative bioavailability of arsenic in sediment samples from the site in order to improve accuracy and decrease uncertainty in human health risk evaluations.

2.0 STUDY DESIGN

This investigation of arsenic relative bioavailability was performed according to the basic design presented in Table 2-1. As shown, the study investigated arsenic absorption from sodium arsenate (the reference material) and from two site-specific sediments, each administered to groups of animals at three different dose levels for 12 days. All doses were administered orally.

2.1 Test Materials

2.1.1 Preliminary Characterization of Site Sediment Samples

Preparation of the two test materials for this study began by collecting 12 sediment samples from multiple locations along the Aberjona River. Each of these samples was characterized in order to support decisions as to which samples should be selected for use as dose material in the animal study, as well as to answer questions about how the dose material should be prepared and administered. Figure 2-1 is a flow chart that summarizes this characterization process.

Sample Description

The sampling locations of the 12 sediment samples span four basic regions of the Aberjona River. Sediment samples 1-3 were collected from the Halls Brook Holding Area, samples 4-6 were collected from the Wells G&H 38-acre Wetland, samples 7-9 were collected from the Cranberry Bog, and samples 10-12 were from Davidson Park. Samples were selected to cover a range of arsenic concentrations in sediments, and were also selected to provide reasonable spatial representativeness across the site.

Sample Preparation

One portion of each of the 12 samples was coarse-sieved through a 1 cm screen to remove large debris (sticks, leaf matter, stones, etc.). This screening was performed on the moist (un-dried) samples. A portion of this coarse-sieved material was removed for arsenic analysis, and a second portion was removed for *in vitro* bioaccessibility analysis (see below). The remaining portion was air dried and fine-sieved (using a 2 mm screen). This step was performed because it is considered probable that the fine-grained portion of the sediment is more likely to adhere to skin and be ingested by humans than the coarse-grained fraction.

Arsenic Concentration

The concentration of arsenic was measured in both the coarse- and fine-sieved samples by inductively coupled plasma atomic absorption spectrometry (ICP-AES). The results from these analyses are shown below:

River Segment	Sample	Arsenic Concentration (ppm)	
		Fine-sieved	Coarse-sieved
Halls Brook Holding Area	1	459	583
	2	527	590
	3	144	269
Wells G&H Wetland	4	145	411
	5	775	605
	6	176	156
Cranberry Bog	7	301	315
	8	832	560
	9	407	388
Davidson Park	10	43.4	37.0
	11	64.0	91.8
	12	67.1	74.9

As seen, the concentration of arsenic in the sediment samples is quite variable, both within a segment of river and between segments. In general, the concentration of arsenic in coarse-sieved and fine-sieved material tends to be similar (Figure 2-2). Thus, RBA results based on tests using fine-sieved material can be extrapolated to samples for which only bulk sample results are available.

In Vitro Bioaccessibility

In vivo absorption of arsenic from a solid medium such as sediment depends on the rate and extent to which arsenic dissolves from the solid medium into the fluids of the gastrointestinal tract. Dr. John Drexler at the University of Colorado has developed a standard procedure to measure the amount of arsenic that dissolves from a test material into a fluid that is similar to the gastric fluid of humans. The amount of arsenic that solubilizes in this test after a specified period of time (usually one hour) is referred to as the *in vitro* bioaccessibility (IVBA), and this value may be used as a preliminary qualitative indicator of potential *in vivo* RBA.

Figure 2-3 shows the IVBA for each of the 12 dried and fine-sieved sediment samples from the site. As seen, there is a range of values, and the IVBA appears to be inversely correlated with concentration (i.e., the most concentrated samples tend to have the lowest *in vitro* bioaccessibility, while the least concentrated samples tend to have the highest *in vitro* bioaccessibility). The basis for this apparent relationship is not known.

Effect of Drying

Each of the sediment samples collected in the field contained considerable moisture content. *A priori*, it was considered possible that drying the samples might alter (increase) the binding of

arsenic to the sediment particles, potentially resulting in a change (decrease) in bioavailability. In order to investigate this possibility, the IVBA of the dried and un-dried samples were compared. Because the moist, un-dried material could not be effectively sieved through the 2mm screen, the moist sample was selected manually to include as few coarse particles as possible. The results are shown in the following table and in Figure 2-4:

River Segment	Sample	*In Vitro* Bioaccessibility of Arsenic (%)	
		Dry	Moist (Un-dried)
Halls Brook Holding Area	1	40	2
	2	31	5
	3	70	5
Wells G&H Wetland	4	40	26
	5	12	16
	6	55	9
Cranberry Bog	7	37	12
	8	13	12
	9	15	13
Davidson Park	10	39	53
	11	49	53
	12	59	9
Average		38	18

As seen, drying the moist material does not appear to significantly influence the IVBA for some samples, and tends to increase rather than decrease the IVBA for other samples. The basis for this apparent change in IVBA is not known, but the results suggest that dried sediment will be as bioavailable or more bioavailable than un-dried sediments. On this basis, it was decided that the *in vivo* test of RBA would be performed using the dried materials.

Evaluation of Methyl Arsenic

Studies at other sites (e.g., Sanders et al. 1994) have revealed that arsenic in sediments may become methylated by microbial action at times when the oxygen tension in the sediments is low. Because methylated forms of arsenic might have different bioavailability (and different toxicity) than the inorganic forms, aliquots of the dried fine-sieved samples were analyzed for organic methyl arsenic. Samples were sent to West Coast Analytical Services, where they were extracted with carbonate buffer and analyzed for As+3, As+5, MMA, and DMA by ion chromatography-ICPMS. The results are summarized below:

Sample	Total Arsenic (ppm)		Extracted Arsenic (WCAS) (ppm)			
	WCAS	Drexler	As+3	DMA	MMA	As+5
1	630	459	ND	ND	ND	20
2	600	527	ND	ND	ND	ND
3	168	144	ND	ND	ND	ND
4	169	145	ND	ND	ND	ND
5	670	775	ND	ND	ND	ND
6	167	176	ND	ND	ND	ND
7	292	301	ND	ND	ND	ND
8	520	832	ND	ND	ND	ND
9	296	407	ND	ND	ND	ND
10	51	43.4	ND	ND	ND	ND
11	87	64	ND	ND	ND	10
12	83	67.1	ND	ND	ND	11
Detection Limit (ppm)	1		5	5	5	5

WCAS = West Coast Analytical Services

As seen, very low levels were observed for each analyte. Recovery of matrix spikes for As+3 and As+5 was poor, suggesting that recoveries of these species may be low. However, recovery of matrix spikes of MMA and DMA were high (89%). These results indicate that if MMA or DMA are present in the samples, they constitute only a very small fraction of the total arsenic.

Mineral Phase Speciation

Each of the 12 dried fine-sieved samples was characterized by electron microprobe analysis (EMPA) in order to provide preliminary data on the identity and relative abundance of the different mineral forms of arsenic present in the samples. The results are summarized in Table 2-2. As seen, these data suggest that arsenic exists mainly in association with particles of iron oxide, iron sulfate, and zinc-iron sulfate. The preliminary data are too limited to draw firm conclusions, but suggest that the presence of iron oxide is associated with higher arsenic concentrations and lower *in vitro* bioaccessibility, and that the presence of the iron-zinc sulfate complexes is associated with lower arsenic concentrations and higher *in vitro* bioaccessibility.

2.1.2 Test Material Selection and Preparation

Test materials for use in the *in vivo* study were selected by considering the results of the preliminary characterization of 12 site sediment samples (Section 2.1.1, above). Specifically, factors that were considered included the concentration level of arsenic in a sample and the degree to which different samples appear to be similar or dissimilar based on speciation and *in vitro* bioaccessibility testing. Based on the conclusion that the only clear pattern of difference among samples is the *in vitro* bioaccessibility (inversely related to concentration), three test materials were prepared by compositing samples with similar arsenic concentrations, as described below.

Test Material 1

Test Material 1 was prepared by compositing equal masses of dried fine-sieved material from samples 2, 5, and 8. These three samples were selected because they have the highest measured arsenic concentration values (all >500 ppm) and they tend to have low bioaccessibility (average = 19%). In addition, the three samples represent each of the three reaches of river (excluding the Davidson Park area), providing good spatial representativeness. These samples tend to be relatively enriched in the iron oxide form of arsenic.

Test Material 2

Test Material 2 was prepared by compositing equal masses of dried fine-sieved material from samples 1, 6, and 7. These three samples were selected because they have intermediate arsenic concentration values (180-460 ppm), intermediate bioaccessibility values (average = 44%), and represent each of the three upstream reaches of the river. These samples tend to be relatively enriched in the zinc-iron sulfate form of arsenic.

Test Material 3

Test Material 3 was prepared by compositing equal masses of all samples with an arsenic concentration less than 150 ppm (samples 3, 4, 10, 11, and 12). These are the samples with the highest apparent bioaccessibility (average = 51%), but the arsenic levels are too low (average = 93 ppm) to permit effective testing in animals. Although Test Material 3 was not used in the *in vivo* portion of the study, it underwent all of the same detailed characterization efforts as Test Materials 1 and 2.

Test Material Preparation

Each test material was prepared by combining equal masses of the appropriate sediment samples, as indicated above. The samples for a given test material were composited using a stainless steel bowl and mixing spoon, and characterized as detailed below.

2.1.3 Detailed Characterization of Test Materials

Arsenic Concentration

After compositing, the concentration of arsenic in each test material was measured by ICP/AES and by ICP/MS. The results are shown below:

Analytical Method	Arsenic Concentration (mg/kg)		
	TM1	TM2	TM3
ICP/MS	590	290	80
ICP/MS	652	318	93.6
ICP/AES	733	319	–
ICP/AES	730	324	–
Average	676.3	312.8	86.8
Standard Deviation	68.6	15.4	9.6

– = Not measured

Concentration of Other Inorganics, Organic Carbon, and Sulfide

Each sample was analyzed for EPA's Target Analyte List (TAL) of inorganic chemicals, as well as for total organic content (TOC) and total sulfide content. Results are shown in Table 2-3.

Particle Speciation, Size, and Matrix Association

Each test material was characterized by electron microprobe analysis (EMPA) in order to identify the different mineral forms of arsenic that were present in the sample and to estimate how much of the total arsenic was present in each form. In addition, the size distribution of the particles was characterized along with the matrix association of each particle. The detailed data are presented in Appendix A and the results are summarized below.

Arsenic Phases

Speciation of the three test materials indicated that the arsenic in these samples is associated with four different types of mineral phase: iron oxide, iron pyrite, iron sulfate, and zinc sulfate. Estimates of the relative arsenic mass (an approximation of the fraction of the total arsenic present in each phase) are presented below:

Arsenic Speciation Data

Test Material	Number of Particles Counted	Relative Arsenic Mass			
		Iron Oxide	Pyrite	Iron Sulfate	Zinc Sulfate
TM1	186	69%	0%	29%	2%
TM2	123	16%	2%	27%	55%
TM3	57	24%	1%	59%	16%

As seen, arsenic in primarily associated with iron oxide in TM1, with zinc sulfate in TM2, and iron sulfate in TM3. These differences in mineral phase may influence the RBA of the arsenic in the materials.

It is important to note that these quantitative estimates of relative arsenic mass are based on examination of a limited number of arsenic-bearing particles in each sample (N = 57 to 186). Consequently, the quantitative values reported should not be considered to be highly precise, and apparent differences between samples may be partly due to random variation in the analysis rather than authentic differences in composition.

Particle Size Distribution

Particle size is a potentially important contributor to RBA because the fraction of a particle that undergoes dissolution in gastrointestinal fluids is likely related to the surface area to volume ratio (this ratio is larger for small particles than large particles). The distribution of particle sizes for arsenic-bearing grains in these test materials is summarized below:

Particle Size Distribution

Test Material	Percent of Particles by Size Class		
	≤25 um	26-100 um	>100 um
TM1	79%	15%	6%
TM2	85%	14%	2%
TM3	72%	26%	2%

As seen above, in these test materials, a large majority of all arsenic-containing particles are small: an average of 79% of all particles are 25 um or less in size. This predominance of small particles may tend to increase the RBA compared to what would be expected for larger particles of similar composition.

Matrix Association

Arsenic-containing particles may be characterized according to their association with other particles into four types, as follows:

Matrix Association	Description
Liberated	A grain of arsenic-containing material that is not attached to or contained within any other particle
Rimming	Arsenic is present on the outer surface of a particle, usually as a consequence of adsorption or precipitation
Cemented	The arsenic-containing particle is loosely bound to or associated with other particles or phases that do not contain arsenic
Included	The arsenic-containing particle is entirely contained within another particle

In the first three types of matrix association, the arsenic is exposed at the surface of some or all of the particle, and hence the arsenic is available to be dissolved by gastrointestinal fluids. Particles that are fully included in other particles are not exposed to external fluids and are not likely to have high bioavailability. The distribution of matrix associations for arsenic-bearing particles in the test materials from this site is summarized below:

Particle Matrix Associations

Test Material	Percent of Particles by Matrix Class			
	Liberated	Rimming	Cemented	Included
TM1	27%	2%	67%	4%
TM2	22%	0%	78%	0%
TM3	37%	11%	53%	0%

As seen, relative few particles are fully included, and 96-100% of the particles are entirely or partially exposed to external fluids. This suggests that the RBA of the arsenic is likely to be determined primarily by mineral phase and/or particle size rather than by matrix association.

In Vitro Bioaccessibility

The details of the method used to measure the *in vitro* bioaccessibility of arsenic are described in USEPA (1999). In brief, 1.00 g of test substrate is placed into a 125-mL wide-mouth HDPE bottle. To this is added 100 mL of the extraction fluid (0.4 M glycine, pH 1.5). Each bottle is placed into a heated water bath (water temperature = 37°C) and rotated end-over-end. After a specified period of time (1, 2 or 4 hours), the bottles are removed, dried, and placed upright on the bench top to allow the soil to settle to the bottom. A 15-mL sample of supernatant fluid is removed directly from the extraction bottle into a disposable 20-cc syringe. After withdrawal of the sample into the syringe, a Luer-Lok attachment fitted with a 0.45-µm cellulose acetate disk filter (25 mm diameter) is attached, and the 15 mL aliquot of fluid is filtered through the attachment to remove any particulate matter. This filtered sample of extraction fluid is then analyzed for arsenic. The fraction of arsenic originally present in the sample that occurs in the dissolved phase at the end of the extraction procedure is the *in vitro* bioaccessibility (IVBA). IVBA results for the three test materials in this study are summarized below:

Test Material	Concentration (ppm)	IVBA		
		1 hr.	2 hr.	4 hr.
TM1	676	14%	16%	19%
TM2	313	35%	47%	51%
TM3	86.8	49%	57%	66%

As seen, IVBA values tend to increase slowly as a function of extraction time. In all cases, an inverse relationship is observed between IVBA and arsenic concentration in the sediment

sample, similar to the pattern that was observed previously during the preliminary characterization of the 12 site sediments samples (see Section 2.1, above).

2.2 Experimental Animals

Young swine were selected for use in these studies because they are considered to be a good physiological model for gastrointestinal absorption in children (Weis and LaVelle 1991). The animals were intact males of the Pig Improvement Corporation (PIC) genetically defined Line 26, and were purchased from Chinn Farms, Clarence, MO.

The animals were housed in individual stainless steel cages. All animals were held for several days prior to beginning exposure to test materials in order to allow them to adapt to their new environment and to ensure that all of the animals were healthy. Animals were assigned to dose groups at random. When exposure began (day zero), the animals were about 6 weeks old and weighed an average of about 12.1 kg. Animals were weighed every three days during the course of the study. On average, animals gained about 0.4 kg/day and the rate of weight gain was comparable in all groups, ranging from 0.38 to 0.46 kg/day. These body weight data are summarized in Figure 2-5.

2.3 Diet

Animals provided by the supplier were weaned onto standard pig chow purchased from MFA Inc., Columbia, MO. In order to minimize arsenic exposure from the diet, the animals were gradually transitioned from the MFA feed to a special feed (Zeigler Brothers, Inc., Gardners, PA) over the time interval from day -7 to day -3, and this feed was then maintained for the duration of the study. The feed was nutritionally complete and met all requirements of the National Institutes of Health-National Research Council. The typical nutritional components and chemical analysis of the feed is presented in Table 2-4. Each day every animal was given an amount of feed equal to 5% of the mean body weight of all animals on study. Feed was administered in two equal portions of 2.5% of the mean body weight at each feeding. Feed was provided at 11:00 AM and 5:00 PM daily. Previous analysis of feed samples indicated the arsenic level was generally below the detection limit (0.1 ppm), which corresponds to a dose contribution from food of less than 5 ug/kg-day (less than 50 ug/day).

Drinking water was provided *ad libitum* via self-activated watering nozzles within each cage. Previous analysis of samples from randomly selected drinking water nozzles indicated the arsenic concentration was less than the quantitation limit (about 1 ug/L). Assuming water intake of about 0.1 L/kg-day, this corresponds to a dose contribution from water of less than 0.1 ug/kg-day (1 ug/day).

2.4 Dosing

Animals were exposed to sodium arsenate (abbreviated in this report as "NaAs") or a test material (site sediment) for 12 days, with the dose for each day being administered in two equal portions given at 9:00 AM and 3:00 PM (two hours before feeding). Dose material was placed in the

center of a small portion (about 5 grams) of moistened feed (this is referred to as a "doughball"), and this was administered to the animals by hand.

The dose levels administered were based on the arsenic content of the test material, with target doses of 300, 600, and 900 ug/day for NaAs and each test material. The mass of each test material needed to provide these doses of arsenic were calculated based on a preliminary estimation of the arsenic concentration in the test materials. Actual administered arsenic doses were re-calculated after the study was completed using the mean of two ICP-AES measurements and two ICP-MS measurements. These actual administered doses are presented in Appendix B.

2.5 Collection and Preparation of Samples

Urine

Samples of urine were collected from each animal for three consecutive 48-hour periods, on days 6/7, 8/9 and 10/11 of the study. Collection began at 9AM and ended 48 hours later. The urine was collected in a stainless steel pan placed beneath each cage, which drained into a plastic storage bottle. Each collection pan was fitted with a nylon screen to minimize contamination with feces, spilled food, or other debris. Plastic diverters were used to minimize urine dilution with drinking water spilled by the animals from the watering nozzle into the collection pan, although this was not always effective in preventing dilution of the urine with water. Due to the length of the collection period, collection containers were emptied at least twice daily into a separate holding container. This ensured that there was no loss of sample due to overflow.

At the end of each collection period, the urine volume was measured and 60-mL portions were removed for analysis. A separate 250-mL aliquot was retained as an archive sample. Each sample was acidified by the addition of concentrated nitric acid. The samples were stored refrigerated until arsenic analysis.

2.6 Arsenic Analysis

Urine samples were assigned random sample numbers and submitted to the laboratory for analysis in a blind fashion. Details of urine sample preparation and analysis are provided in USEPA (1999). In brief, 25 mL samples of urine were digested by refluxing and then heating to dryness in the presence of magnesium nitrate and concentrated nitric acid. Following magnesium nitrate digestion, samples were transferred to a muffle furnace and ashed at 500°C. The digested and ashed residue was dissolved in hydrochloric acid and analyzed by the hydride generation technique using a Perkin-Elmer 3100 atomic absorption spectrometer. Preliminary tests of this method established that each of the different forms of arsenic that may occur in urine, including trivalent inorganic arsenic (As+3), pentavalent inorganic arsenic (As+5), monomethyl arsenic (MMA) and dimethyl arsenic (DMA), are all recovered with high efficiency.

Laboratory Quality Assurance

A number of quality assurance steps were taken during this project to evaluate the accuracy of the analytical procedures. Steps performed by the analytical laboratory included:

Spike Recovery

Randomly selected samples were spiked with known amounts of arsenic (usually 40 ug, as sodium arsenate) and the recovery of the added arsenic was measured. Recovery for individual samples ranged from 95% to 110%, with an average across all analyses of 103 ± 4.5% (N = 7).

Duplicate Analysis

Random samples were selected for duplicate analysis by the laboratory analyst. Duplicate results had a relative percent difference (RPD) of 0-17%, with an average of 2.6 ± 5.0% (N = 13).

Laboratory Control Standards

Four different types of laboratory control standards (LCS) were tested periodically during the analysis. These are samples for which a certified concentration of arsenic has been established. Results for these four types of LCS are summarized below:

LCS Type	Certified Value	Average Recovery	SEM	N
E.R.A. P081 - Metals WasteWatR	366 ng/mL	97%	1.7%	42
N.R.C.C. Dolt-2 Dogfish Liver	16.6 +/- 1.1 ug/g dry wt	84%	0.0%	2
N.R.C.C. Tort-2 Lobster	21.6 +/- 1.8 ug/g dry wt	99%	3.3%	3
N.I.S.T. Oyster 1566b	7.65 +/- 0.65 ug/g dry wt	97%	0.8%	3

As seen, recovery of arsenic from these standards was good in all cases, and no samples were outside the acceptance criteria specified by the suppliers.

Blanks

Blank samples run along with each batch of samples never yielded a measurable level of arsenic, with all values being reported as less than 0.03 ug of arsenic.

Blind Quality Assurance Samples

In addition to these laboratory-sponsored QA samples, an additional series of QA samples were submitted to the laboratory in a blind fashion. This included a number of Performance Evaluation (PE) samples (urines of known arsenic concentration) and a number of blind duplicates.

The results for the PE samples are shown in Figure 2-6. As seen, the PE samples included several different concentrations each of four different types of arsenic (As+3, As+5, MMA, and DMA). In all cases, there was good recovery of the arsenic.

The results for blind duplicates are shown in Figure 2-7. As seen, there was good agreement between results for the duplicate pairs.

Based on the results of all of the quality assurance samples and steps described above, it is concluded that the analytical results for samples of urine are of high quality and are suitable for derivation of reliable estimates of arsenic absorption from test materials.

3.0 DATA ANALYSIS

Figure 3-1 shows a conceptual model for the toxicokinetic fate of ingested arsenic. Key points of this model are as follows:

- In most animals (including humans), absorbed arsenic is excreted mainly in the urine over the course of several days. Thus, the urinary excretion fraction (UEF), defined as the amount excreted in the urine divided by the amount given, is usually a reasonable approximation of the oral absorption fraction or ABA. However, this ratio will underestimate total absorption, because some absorbed arsenic is excreted in the feces via the bile, and some absorbed arsenic enters tissue compartments (e.g., skin, hair) from which it is cleared very slowly or not at all. Thus the urinary excretion fraction should not be equated with the absolute absorption fraction.

- The relative bioavailability (RBA) of two orally administered materials (i.e., test material and reference material) can be calculated from the ratio of the urinary excretion fraction of the two materials. This calculation is independent of the extent of tissue binding and of biliary excretion:

$$RBA(test\ vs\ ref) = \frac{AF_o(test)}{AF_o(ref)} = \frac{D \cdot AF_o(test) \cdot K_u}{D \cdot AF_o(ref) \cdot K_u} = \frac{UEF(test)}{UEF(ref)}$$

Based on the conceptual model above, raw data from this study were reduced and analyzed as follows:

- The amount of arsenic excreted in urine by each animal over each collection period was calculated by multiplying the urine volume by the urine concentration:

$$\text{Excreted (ug/48hr)} = \text{Concentration (ug/L)} \cdot \text{Volume (L/48hr)}$$

- For each test material, the amount of arsenic excreted by each animal was plotted as a function of the amount administered (ug/48 hours), and the best fit straight line (calculated by linear regression) through the data (ug excreted per ug administered) was used as the best estimate of the urinary excretion fraction (UEF).

- The relative bioavailability of arsenic in a test material was calculated as:

$$\text{RBA} = \text{UEF(test)} / \text{UEF(NaAs)}$$

  where sodium arsenate (NaAs) is used as the frame of reference.

- As noted above, each RBA value is calculated as the ratio of two slopes (UEFs), each of which is estimated by linear regression through a set of data points. Because of the variability in the data, there is uncertainty in the estimated slope (UEF) for each material. This uncertainty in the slope is described by the standard

error of the mean (SEM) for the slope parameter. Given the best estimate and the SEM for each slope, the uncertainty in the ratio may be calculated using Monte Carlo simulation. The probability density function describing the confidence around each slope (UEF) term was assumed to be characterized by a t-distribution with n-2 degrees of freedom :

$$\frac{UEF(measured) - UEF(true)}{SEM} \sim t_{n-2}$$

For convenience, this PDF is abbreviated T(slope, sem, n), where slope = best estimate of the slope derived by linear regression, sem = standard deviation in the best estimate of the slope, and n = number of data points upon which the regression analysis was performed. Thus, the confidence distribution around each ratio was simulated as:

$$PDF(RBA) = \frac{T(slope, sem, n)_{test}}{T(slope, sem, n)_{ref}}$$

Using this equation, a Monte Carlo simulation was run for each RBA calculation. The 5th and 95th percentile values from the simulated distribution of RBA values were then taken to be the 90% confidence interval for the RBA.

4.0 RESULTS

4.1 Clinical Signs

The doses of arsenic administered in this study are below a level that is expected to cause toxicological responses in swine, and no clinical signs of arsenic-induced toxicity were noted in any of the animals used in the study.

4.2 Urinary Excretion Fractions

Detailed results from the study are presented in Appendix B. The results for urinary excretion of arsenic are summarized in Figures 4-1 to 4-3. Although there is variability in the data, most dose-response curves are approximately linear, with the slope of the best-fit straight line being equal to the best estimate of the urinary excretion fraction (UEF). The following table summarizes the best fit slopes (urinary excretion fractions) for sodium arsenate and each of the test materials.

Summary of UEF Values

Test Material	Slope (UEF) ± SEM
NaAs	0.892 ± 0.033
TM1	0.326 ± 0.021
TM2	0.456 ± 0.021

4.3 Calculation of Relative Bioavailability

As discussed above, the relative bioavailability of arsenic in a specific test material is calculated as follows:

$$RBA(\text{test } vs. \text{ NaAs}) = UEF(\text{test}) / UEF(\text{NaAs})$$

The results are summarized below:

Test Material	Relative Bioavailability	
	Best Estimate	90% Confidence Interval
TM1	37%	32% - 41%
TM2	51%	46% - 56%

5.0 DISCUSSION AND RECOMMENDATIONS

The *in vivo* RBA results for two composite sediments collected from the Aberjona River study area range from 37% to 51%. These results clearly indicate that arsenic in Aberjona River site sediments is not as well absorbed as soluble arsenic, and it is appropriate to take this into account when evaluating potential risks to humans from incidental ingestion of sediments. Because each sediment sample tested during this study is a composite of three sub-samples collected from differing locations along the Aberjona River, each test material represents a fairly large spatial area, and the results for these two samples may be assumed to be generally applicable to the entire site.

Although RBA values can be applied in the site risk assessment process without any understanding of what factors are responsible for the observed RBA values, it is a matter of some interest to investigate the degree to which the RBA value is correlated with other factors. The following table compares the measured values for RBA with the arsenic concentration in the sample, the IVBA, and the primary mineral phase present in each test material:

Test Material	Concentration (ppm)	RBA	IVBA		Primary Form
			1 hr	4 hrs	
TM1	676	37%	14%	19%	Iron oxide
TM2	313	51%	35%	51%	Zinc sulfate
TM3	86.8	–	49%	66%	Iron sulfate

As seen, both RBA and IVBA show an inverse correlation with concentration in the sediment. This is plotted graphically in Figure 5-1. The basis of this apparent relationship is not known. Absolute values of IVBA at one hour tend to be lower than the measured RBA values, but the difference between RBA and IVBA tends to decrease after longer extraction times. Although the values for TM2 at 4 hours happen to be equal, the values for TM1 are not equivalent. These data suggest that IVBA is a good screen to evaluate the relative *in vivo* bioavailability of arsenic at different locations, but that it should not be used as a quantitative surrogate for *in vivo* RBA at this site. The data are not sufficient to establish an empiric relationship between mineral form and RBA, but the results suggest that arsenic in association with iron oxide is likely to be less bioavailable that other forms.

6.0 REFERENCES

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TABLE 2-1 STUDY DESIGN

Group	Number of Animals	Material Administered	Target Dose (ug As/day)
1	3	Control	0
2	4	Sodium Arsenate	300
3	4	Sodium Arsenate	600
4	4	Sodium Arsenate	900
5	4	Test Material 1	300
6	4	Test Material 1	600
7	4	Test Material 1	900
8	4	Test Material 2	300
9	4	Test Material 2	600
10	4	Test Material 2	900

TABLE 2-2 PRELIMINARY (SEMI-QUANTITATIVE) SPECIATION RESULTS

Sample	Arsenic Concentration (ppm)	Bioaccesibility (%)	PARTICLE FREQUENCY Phase						PARTICLE SIZE (um) Phase					
			Iron sulfide	Iron oxide	Iron sulfate	Zinc-Iron Sulfate	Tin oxide	Sodium sulfate	Iron sulfide	Iron oxide	Iron sulfate	Zinc-Iron Sulfate	Tin oxide	Sodium sulfate
1	459	40	3	2					2-8	20		5-80		
2	527	31	Tr	2		2		Tr		4-100	8-110	12-25		
3	144	70	3	1		Tr				1-8		8-30		
4	145	40	1		2	1			1-40	8-150	15-125	7-35		
5	775	12	Tr			Tr	Tr			8-250				
6	176	55	3		Tr				3-7			12-40		
7	301	37	3	1	2			2	2-10		3-22	4-80		8-35
8	832	13	Tr			2				35-220		15		
9	407	15				2				30-225		7-30		
10	43.4	39	2	1	Tr				3-7					
11	64.0	49	1		Tr				2-10	15-35				
12	67.1	59	1	1					1-15	14				

Code: 3 = Most Common
2 = Common
1 = Relatively Infrequent
Tr = Trace
= Majority of arsenic in probably in this phase

TABLE 2-3 COMPOSITION OF TEST MATERIALS

Analyte	Concentration (mg/kg)[a]		
	TM1	TM2	TM3
Aluminum	15000	11000	11000
Antimony	4.3	3.7	<1
Arsenic	67.3	31.2	8.38
Barium	75	98	60
Beryllium	0.96	0.62	0.54
Cadmium	15	16	1.9
Calcium	9100	10000	4100
Chromium	680	620	140
Cobalt	32	46	14
Copper	840	540	150
Iron	73000	38000	22000
Lead	410	350	130
Magnesium	2000	2600	4300
Manganese	510	610	430
Mercury	2.9	1.1	0.61
Nickel	28	35	22
Potassium	690	770	1300
Selenium	5.8	3.8	1.6
Silver	0.88	1.1	<1
Sodium	ND	<500	ND
Sulfides, Total	5.9	63	7.2
Thallium	1.7	4.4	1.4
Total Organic Carbon	210 g/kg	220 g/kg	120 g/kg
Vanadium	49	43	35
Zinc	3300	4500	830

ND = Not detected

[a] All values are in units of mg/kg except where noted otherwise. All metals except mercury were measured by USEPA method 6010B. Mercury was measured by USEPA method 7471A, total sulfides were measured by USEPA method 9030B/9034, and total organic carbon was measured by USEPA method 9060. All data are based on single measurements except arsenic, which is based on the average of duplicate analysis by ICP-MS and duplicate analysis by ICP-AES.

Table 2-4 Typical Feed Composition

Nutrient Name	Amount	Nutrient Name	Amount
Protein	20.1021%	Chlorine	0.1911%
Arginine	1.2070%	Magnesium	0.0533%
Lysine	1.4690%	Sulfur	0.0339%
Methionine	0.8370%	Manganese	20.4719 ppm
Met+Cys	0.5876%	Zinc	118.0608 ppm
Tryptophan	0.2770%	Iron	135.3710 ppm
Histidine	0.5580%	Copper	8.1062 ppm
Leucine	1.8160%	Cobalt	0.0110 ppm
Isoleucine	1.1310%	Iodine	0.2075 ppm
Phenylalanine	1.1050%	Selenium	0.3196 ppm
Phe+Tyr	2.0500%	Nitrogen Free Extract	60.2340%
Threonine	0.8200%	Vitamin A	5.1892 kIU/kg
Valine	1.1910%	Vitamin D3	0.6486 kIU/kg
Fat	4.4440%	Vitamin E	87.2080 IU/kg
Saturated Fat	0.5590%	Vitamin K	0.9089 ppm
Unsaturated Fat	3.7410%	Thiamine	9.1681 ppm
Linoleic 18:2:6	1.9350%	Riboflavin	10.2290 ppm
Linoleic 18:3:3	0.0430%	Niacin	30.1147 ppm
Crude Fiber	3.8035%	Pantothenic Acid	19.1250 ppm
Ash	4.3347%	Choline	1019.8600 ppm
Calcium	0.8675%	Pyridoxine	8.2302 ppm
Phos Total	0.7736%	Folacin	2.0476 ppm
Available Phosphorous	0.7005%	Biotin	0.2038 ppm
Sodium	0.2448%	Vitamin B12	23.4416 ppm
Potassium	0.3733%		

Feed obtained from and nutritional values provided by Zeigler Bros., Inc

FIGURE 2-1 SAMPLE CHARACTERIZATION AND PREPARATION FLOW CHART

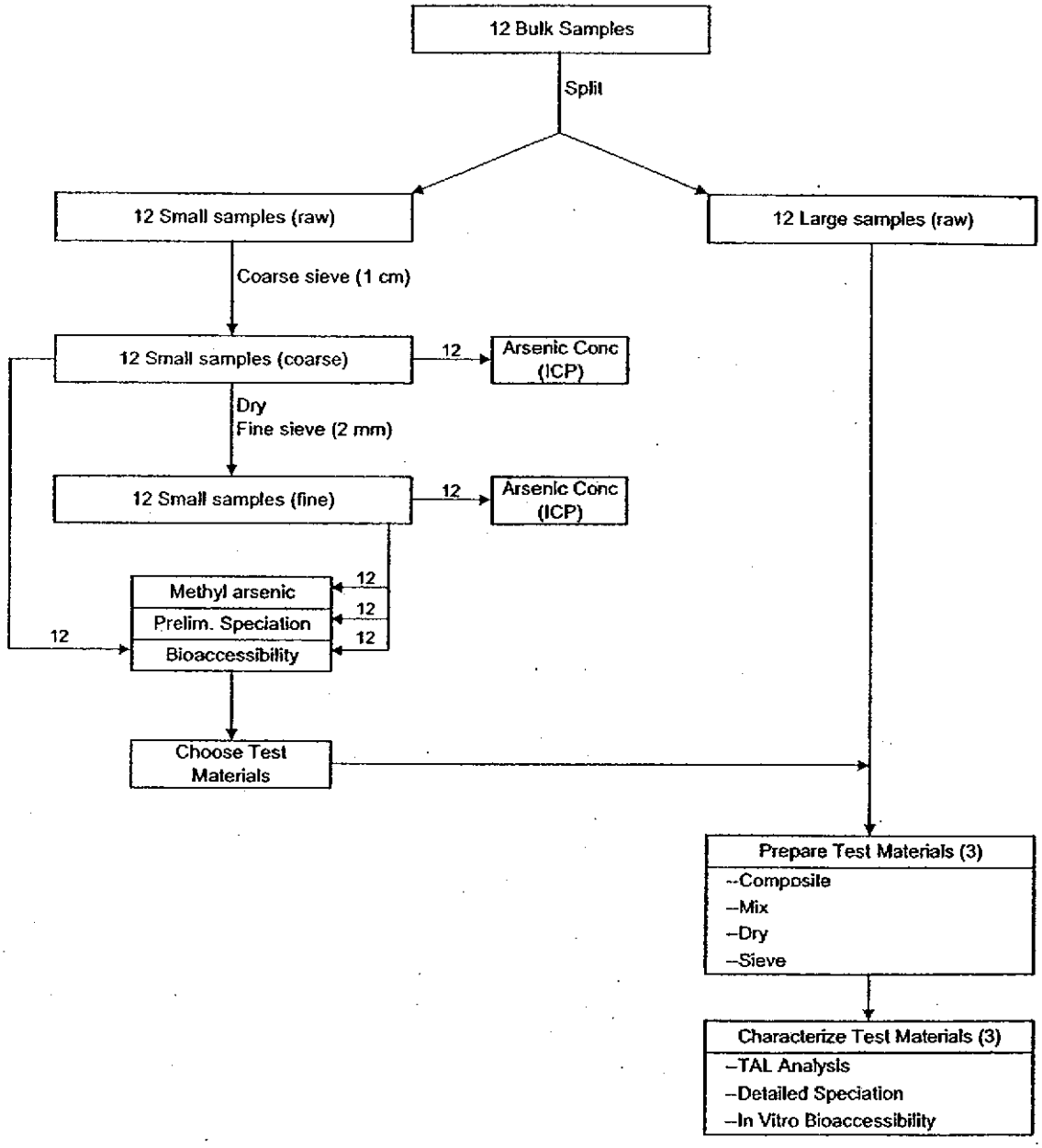
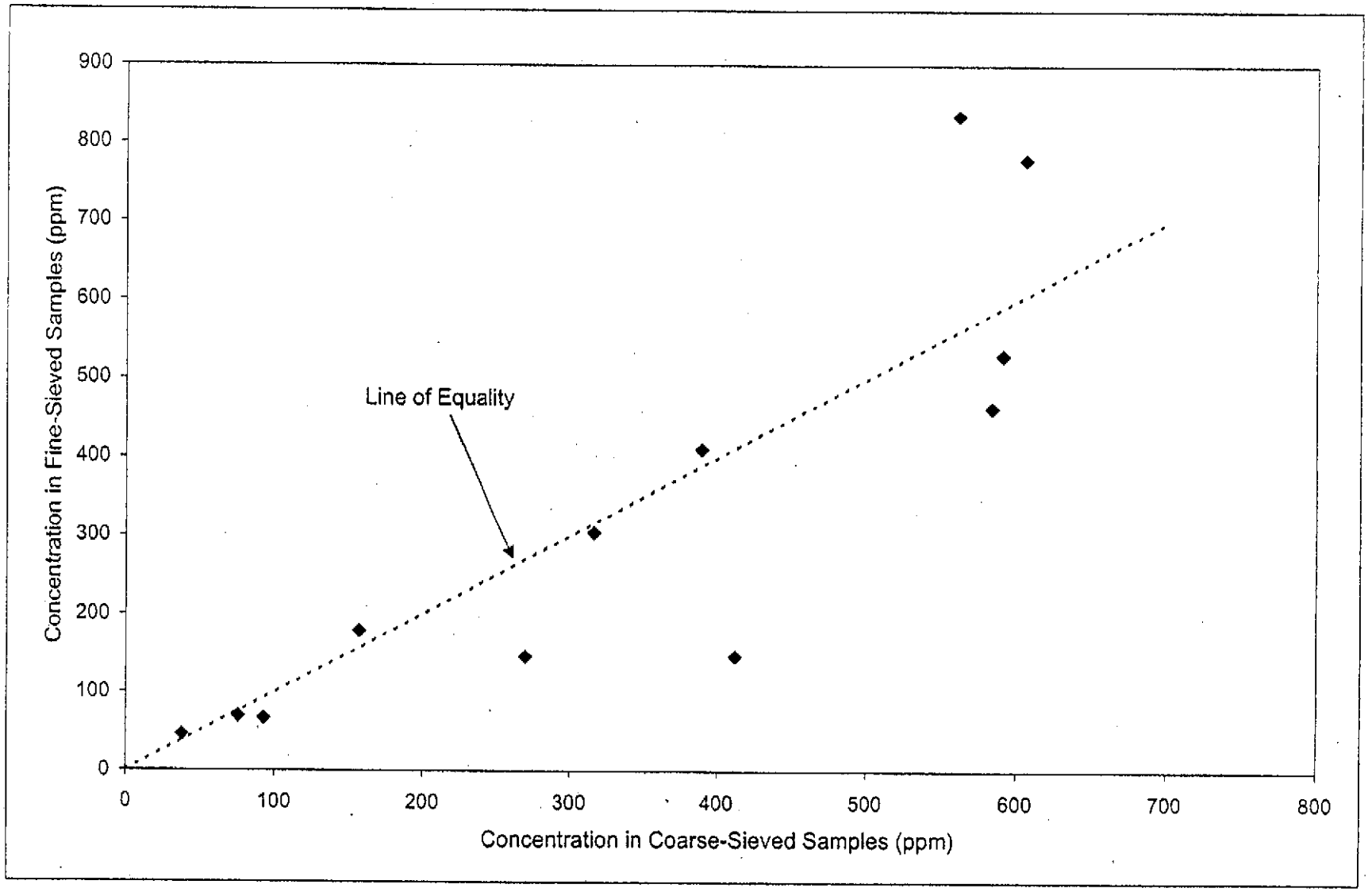


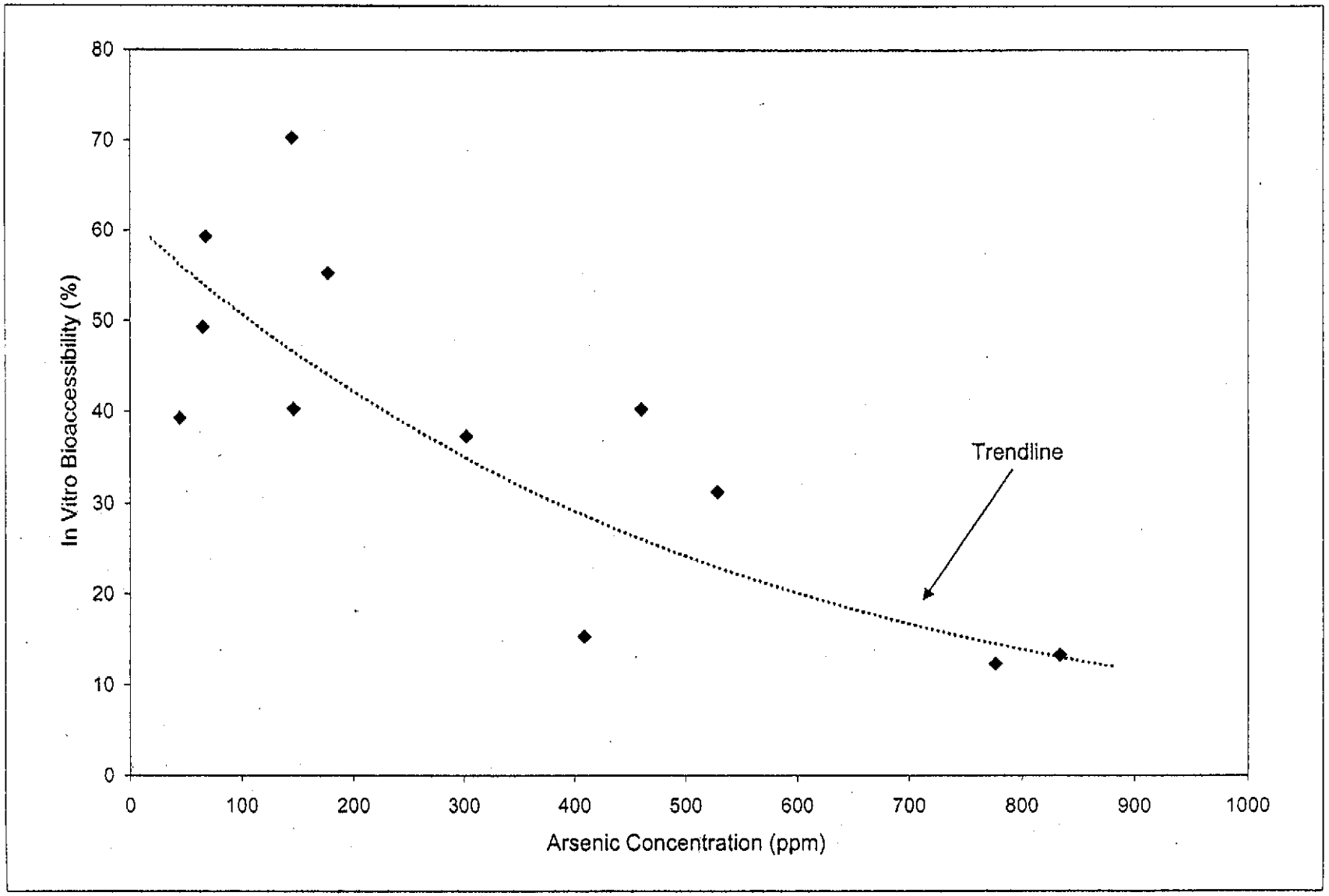
Fig 2-1_Flow Chart.xls

FIGURE 2-2 COMPARISON OF ARSENIC CONCENTRATIONS IN COARSE- AND FINE-SIEVED SAMPLES



Prelim Char_tbls & figs.xls (Fig2-2_coarse-fine)

FIGURE 2-3 IN VITRO BIOACCESSIBILITY OF DRIED FINE-SIEVED SAMPLES



Prelim Char_tbls & figs.xls (Fig2-3_In Vitro)

FIGURE 2-4 COMPARISON OF IN VITRO BIOACCESSIBILITY OF DRIED AND UN-DRIED FINE-SIEVED SAMPLES

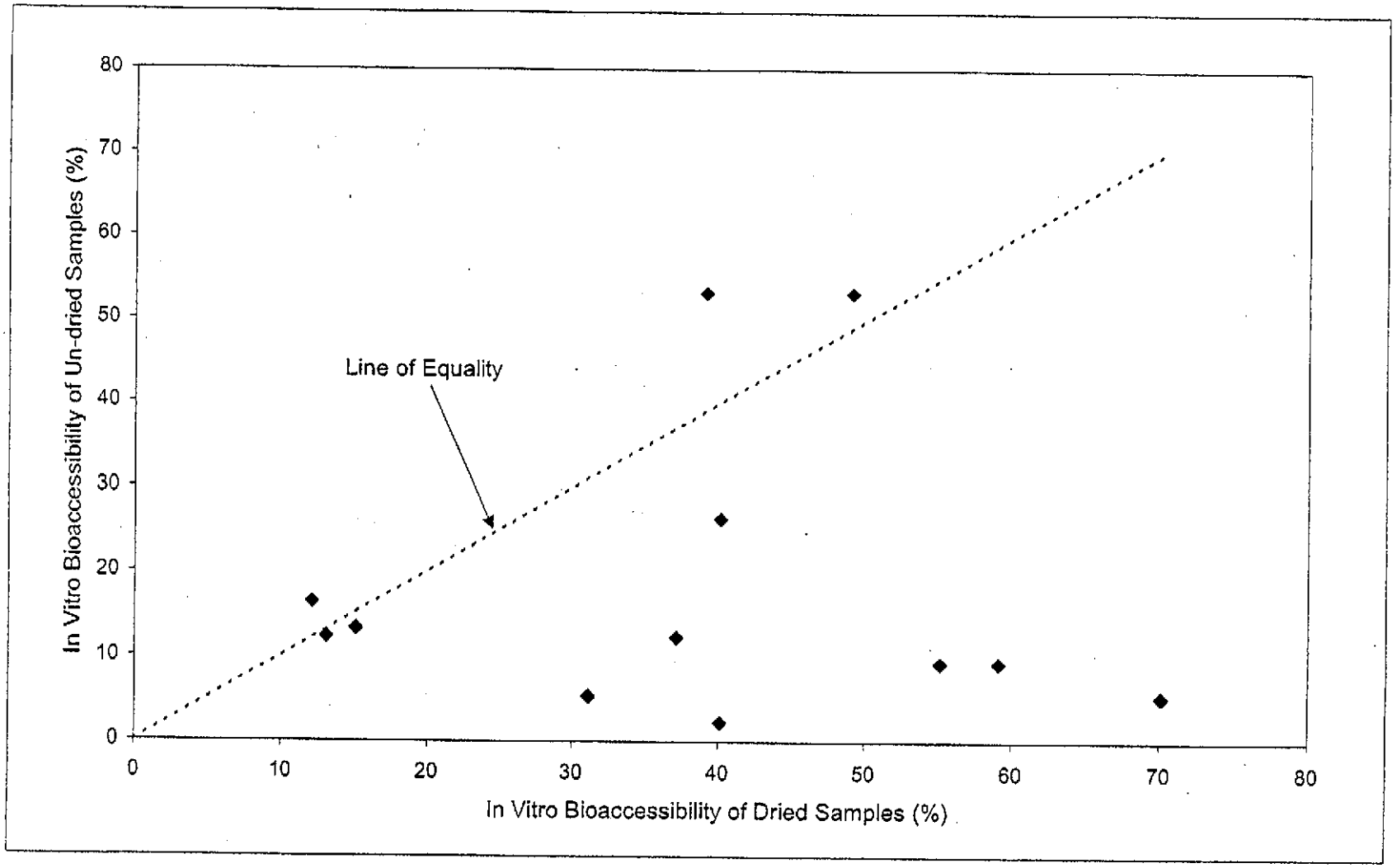
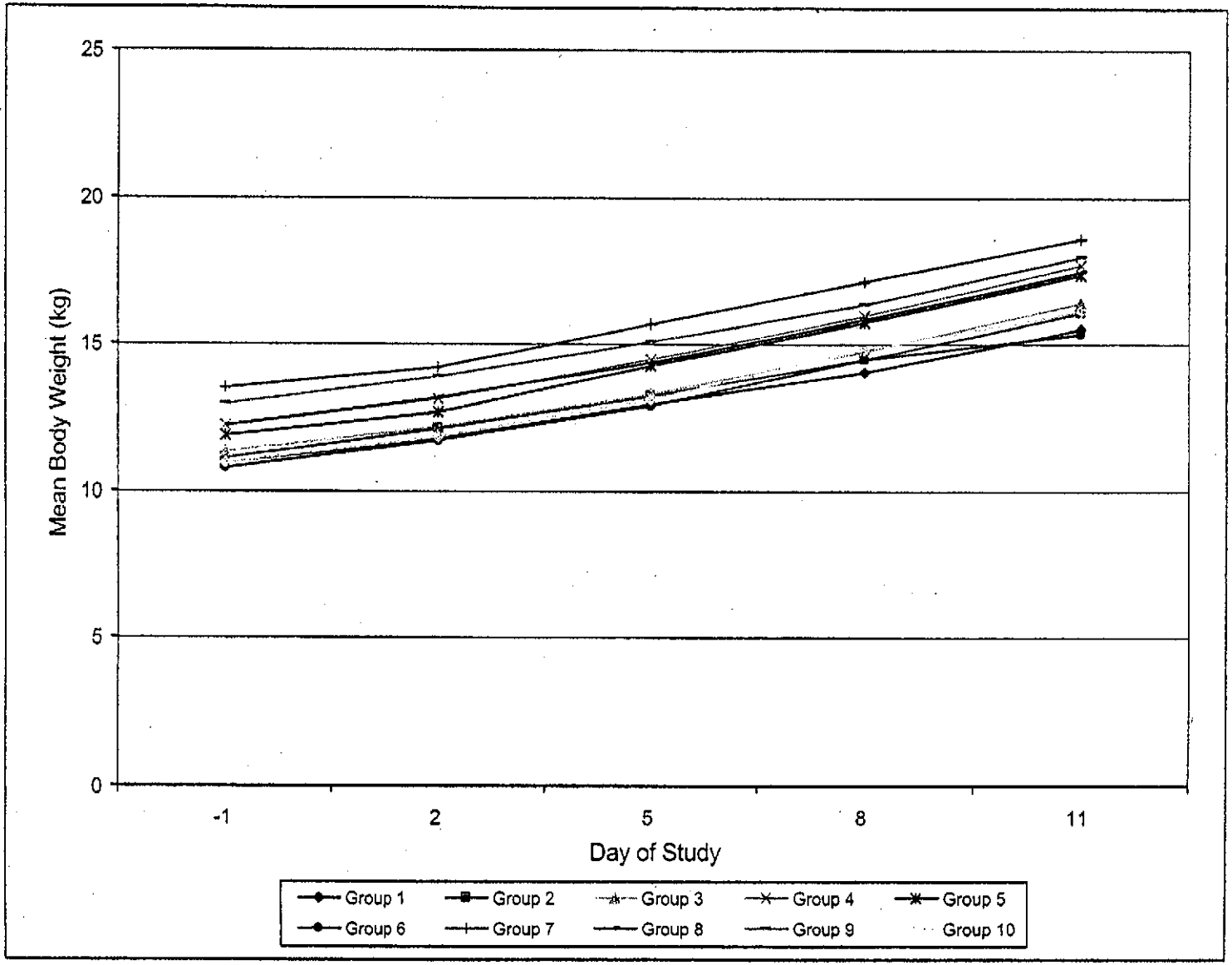
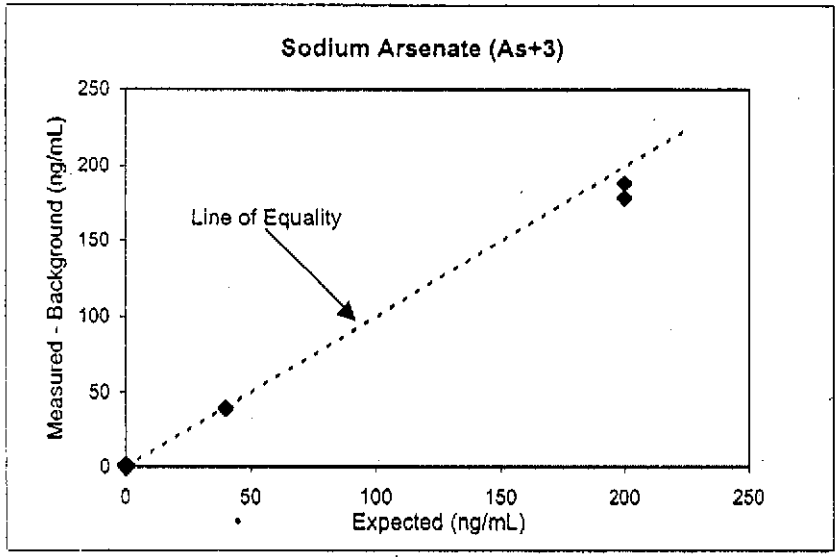


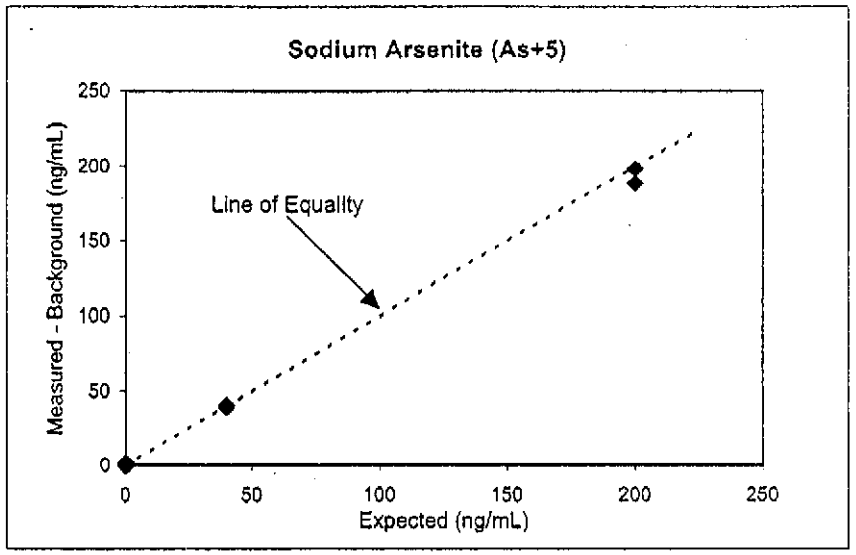
FIGURE 2-5 BODY WEIGHT GAIN

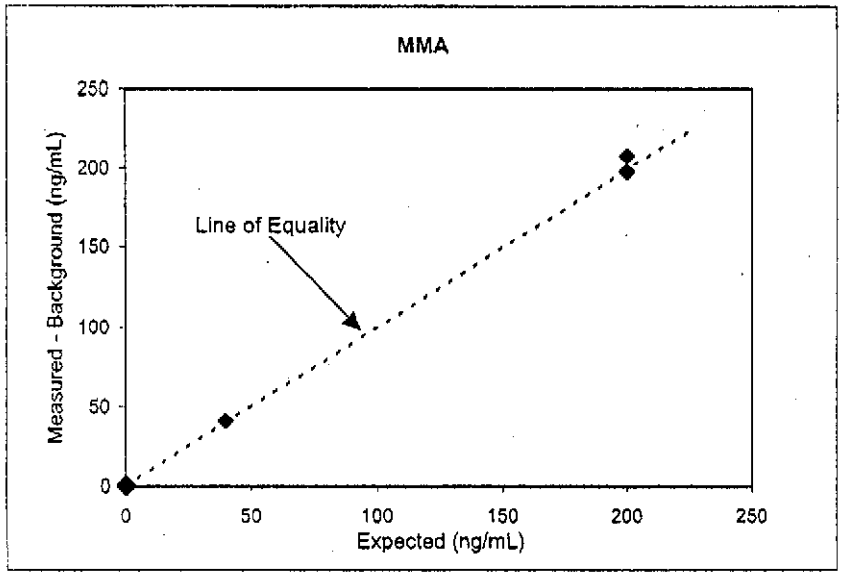


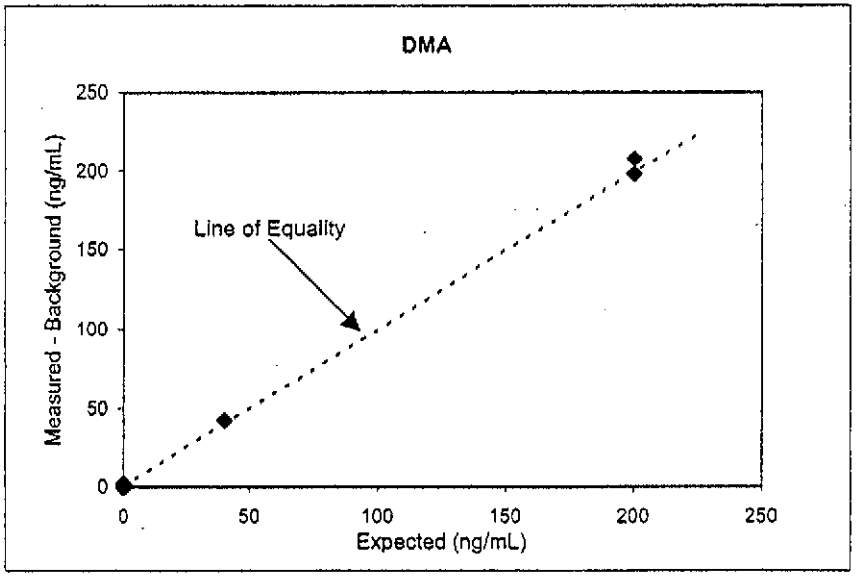
weights.xls (Fig2-5_group weights)

FIGURE 2-6 PERFORMANCE EVALUATION SAMPLES



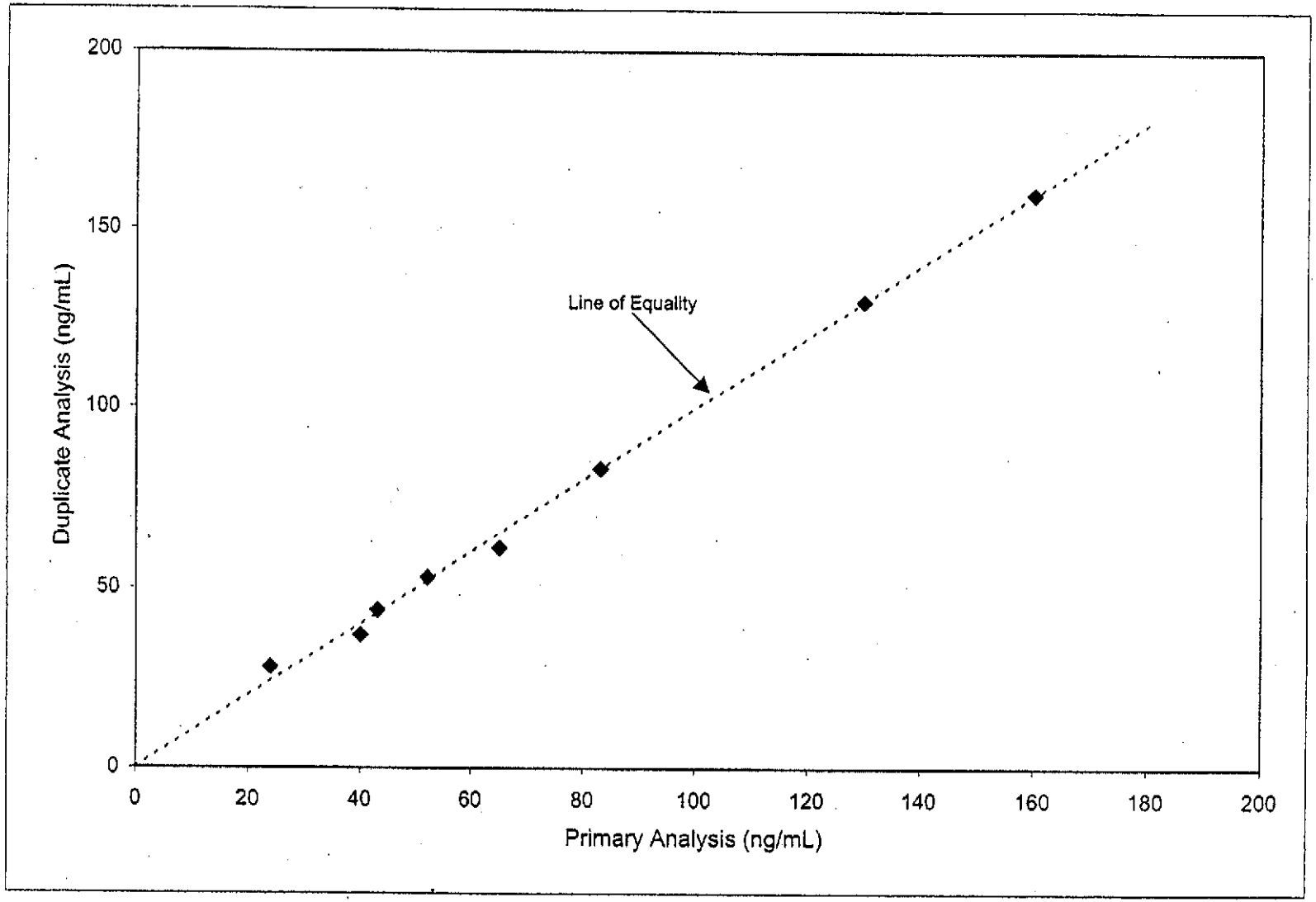






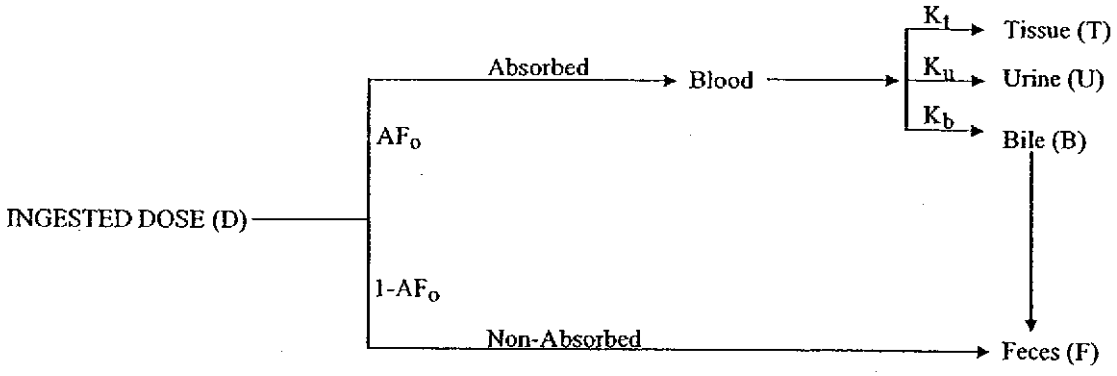
Blind QC analysis.xls (Fig2-6_PE)

FIGURE 2-7 BLIND DUPLICATE SAMPLES



Blind QC analysis.xls (Fig2-7_Dup)

Figure 3-1. Conceptual Model for Arsenic Toxicokinetics



where:

D = Ingested dose (ug)

AF_o = Oral Absorption Fraction

K_t = Fraction of absorbed arsenic which is retained in tissues

K_u = Fraction of absorbed arsenic which is excreted in urine

K_b = Fraction of absorbed arsenic which is excreted in the bile

BASIC EQUATIONS:

Amount Absorbed (ug) $= D \cdot AF_o$

Amount Excreted (ug) $=$ Amount absorbed $\cdot K_u$

$= D \cdot AF_o \cdot K_u$

Urinary Excretion Fraction (UEF) $=$ Amount excreted / Amount ingested

$= (D \cdot AF_o \cdot K_u) / D$

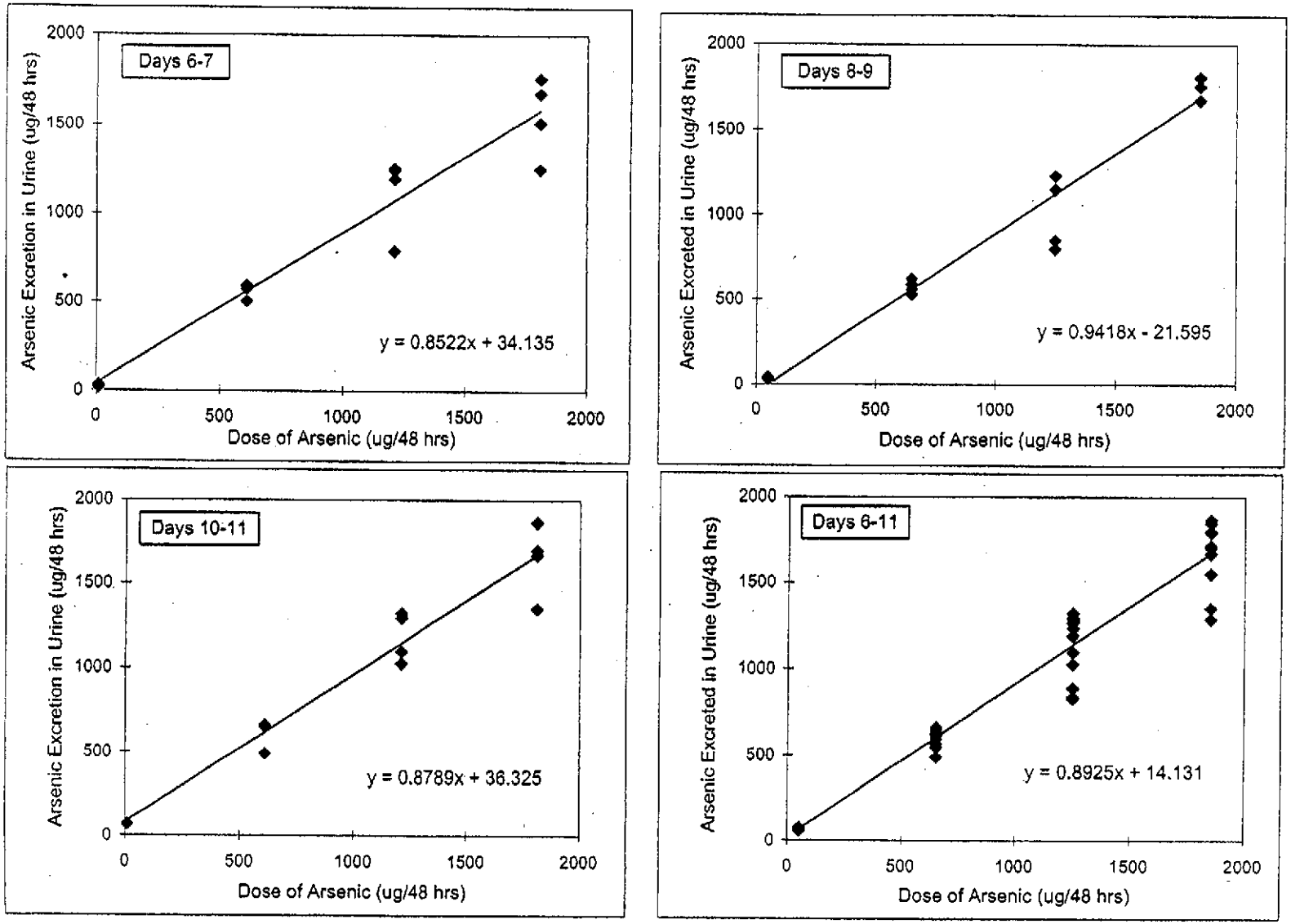
$= AF_o \cdot K_u$

Relative Bioavailability (x vs. y) $= UEF(x) / UEF(y)$

$= (AF_o(x) \cdot K_u) / (AF_o(y) \cdot K_u)$

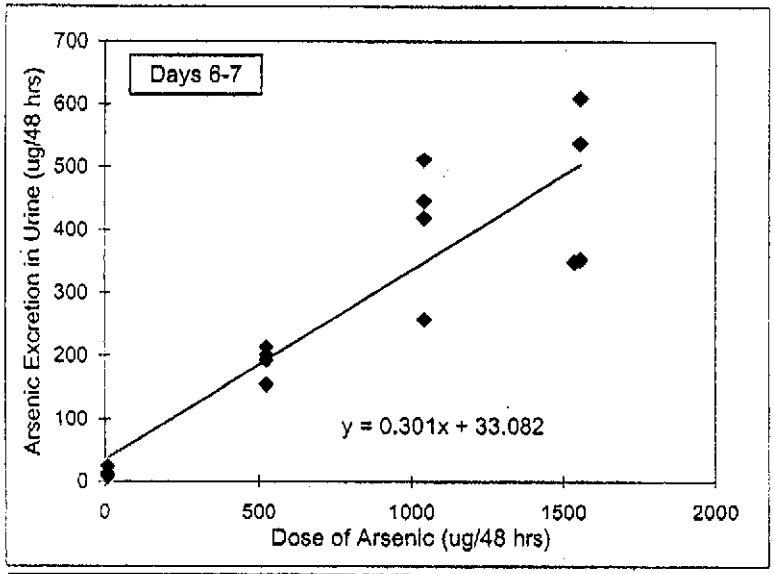
$= AF_o(x) / AF_o(y)$

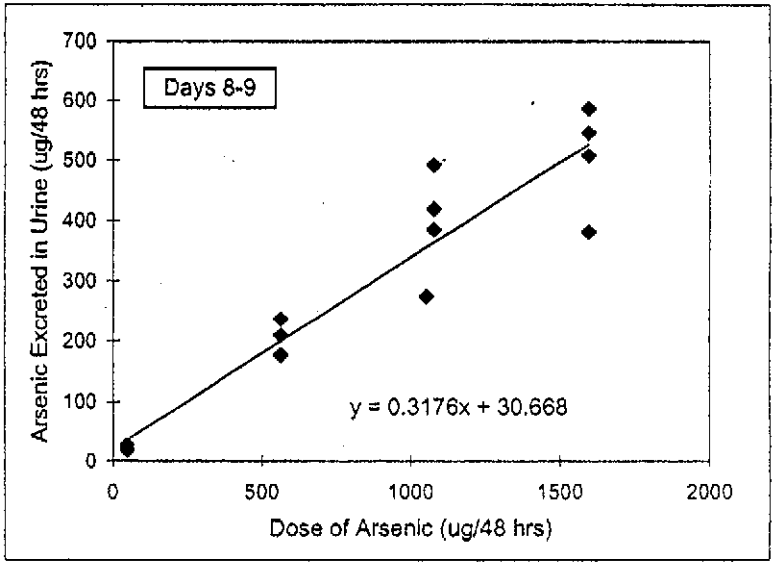
FIGURE 4-1 URINARY EXCRETION OF ARSENIC FROM SODIUM ARSENATE

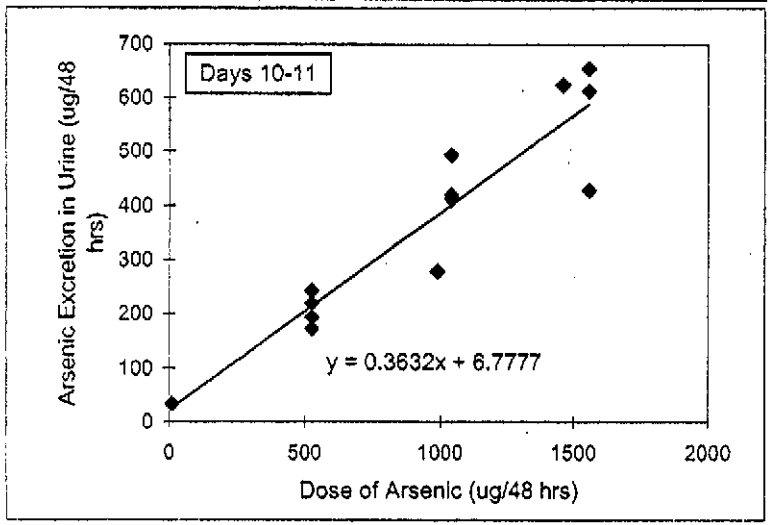


R1 UEF analysis.xls (NaAs)
12/16/2002

FIGURE 4-2 URINARY EXCRETION OF ARSENIC FROM TEST MATERIAL 1







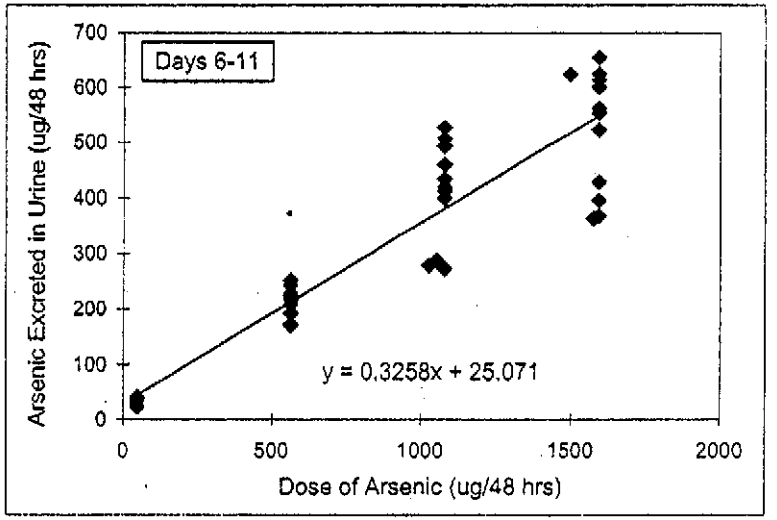
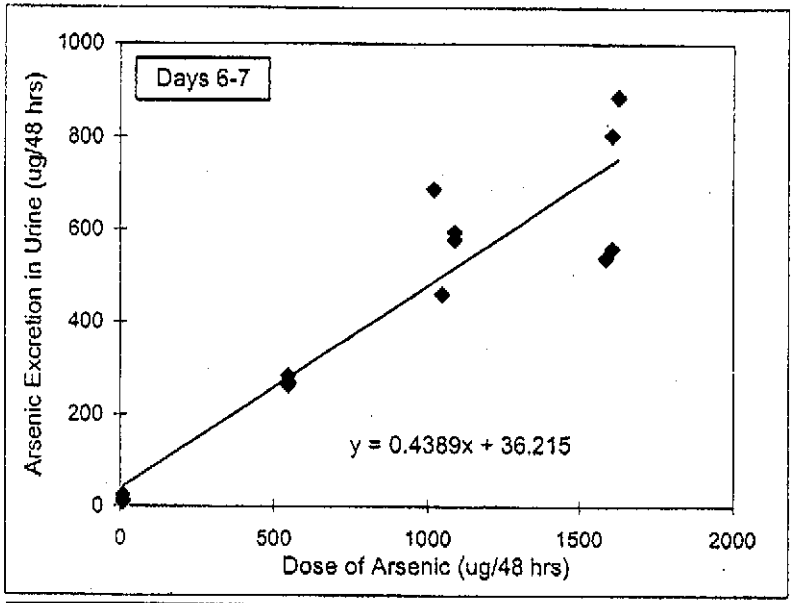
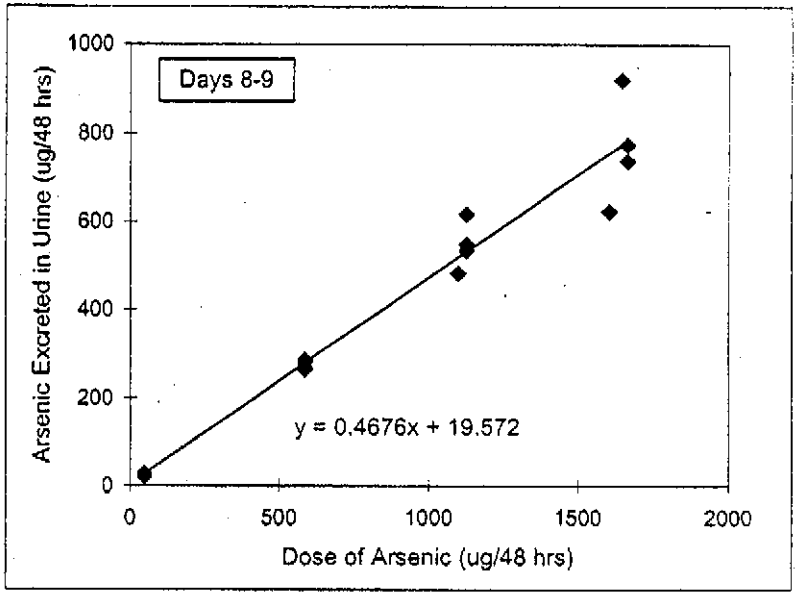
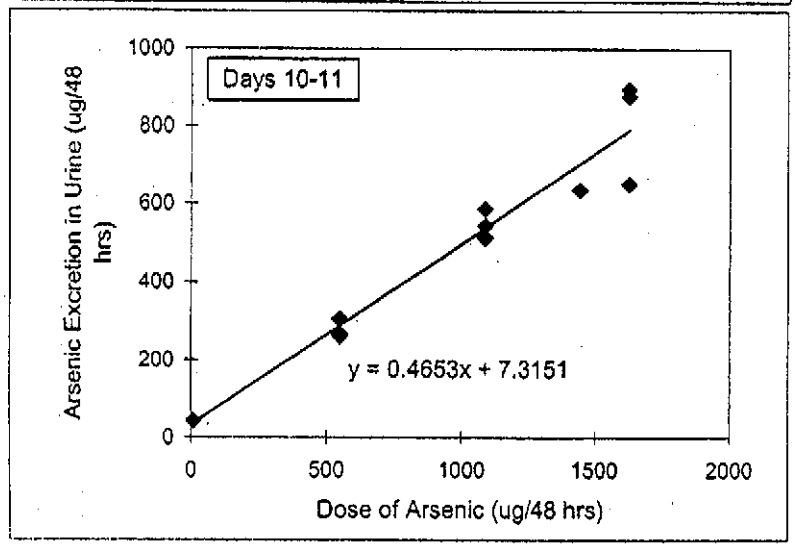


FIGURE 4-3 URINARY EXCRETION OF ARSENIC FROM TEST MATERIAL 2







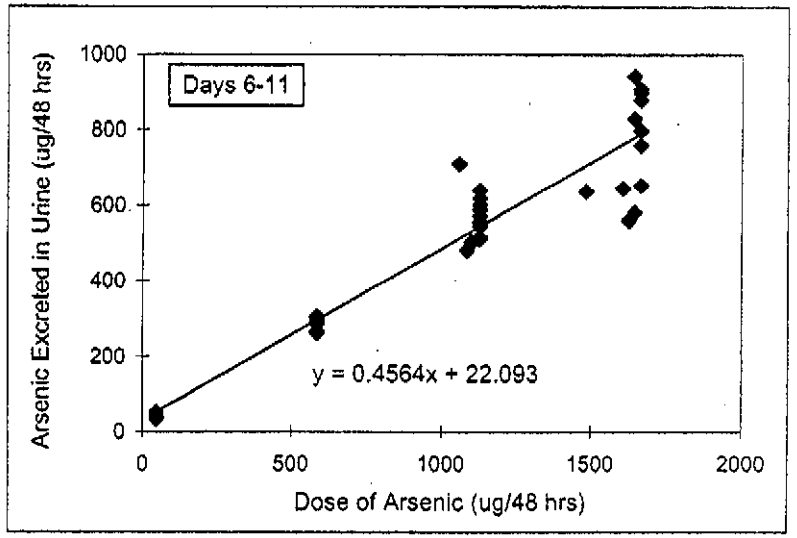
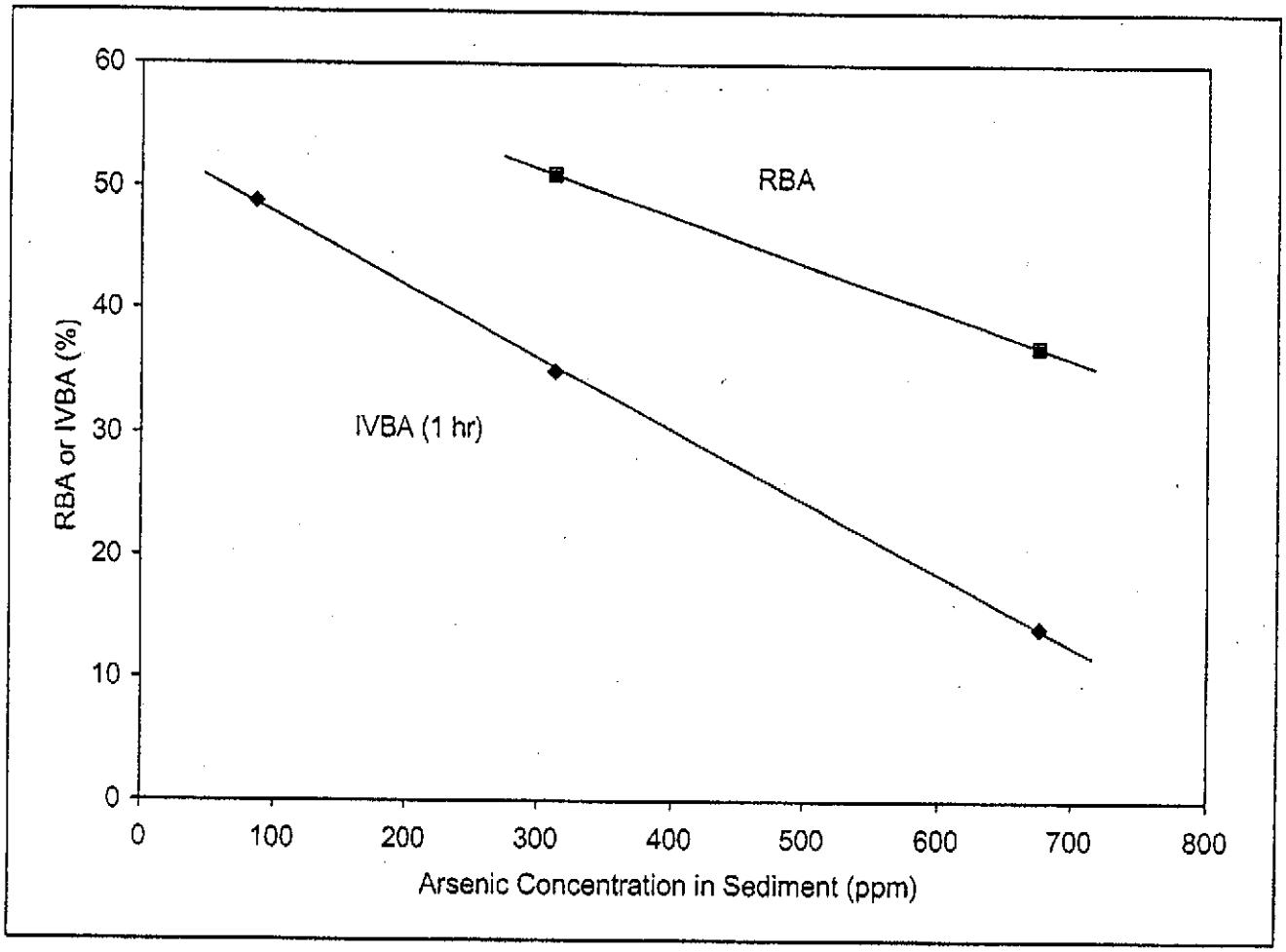


Figure 5-1. RBA and IVBA as a Function of Sediment Concentration

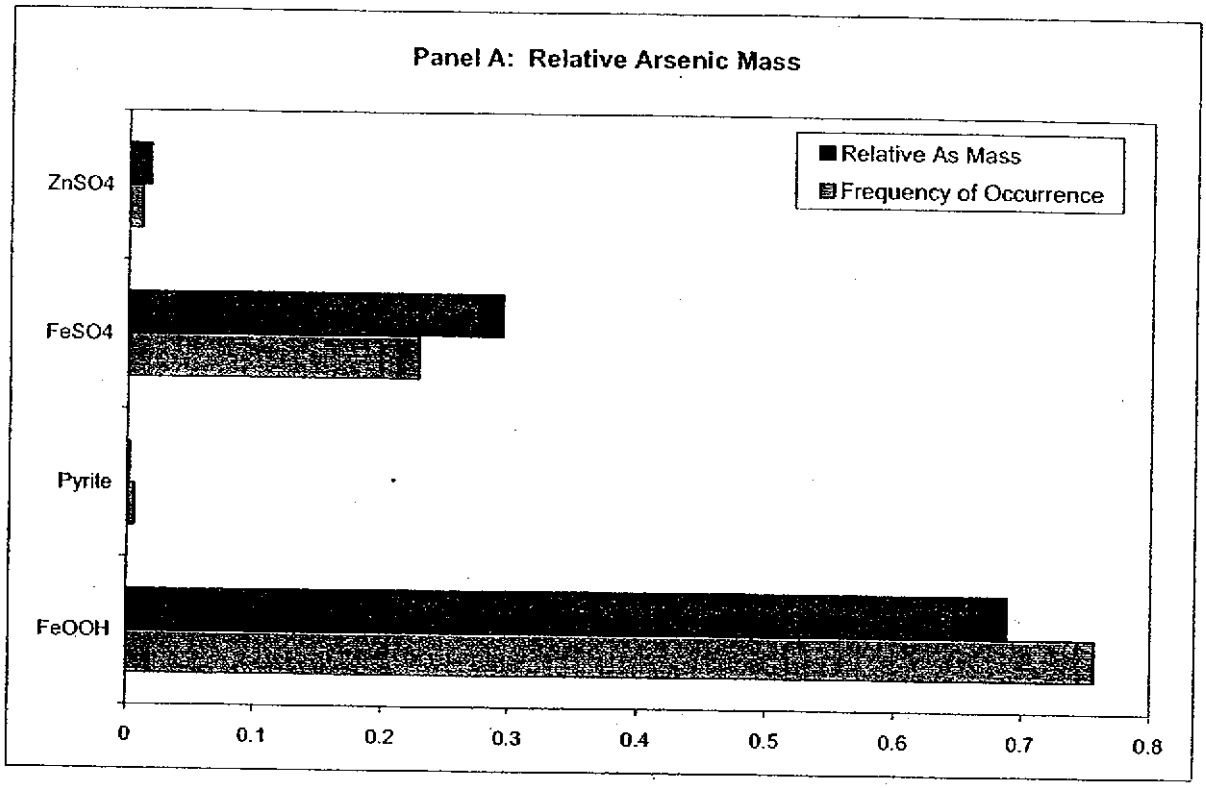


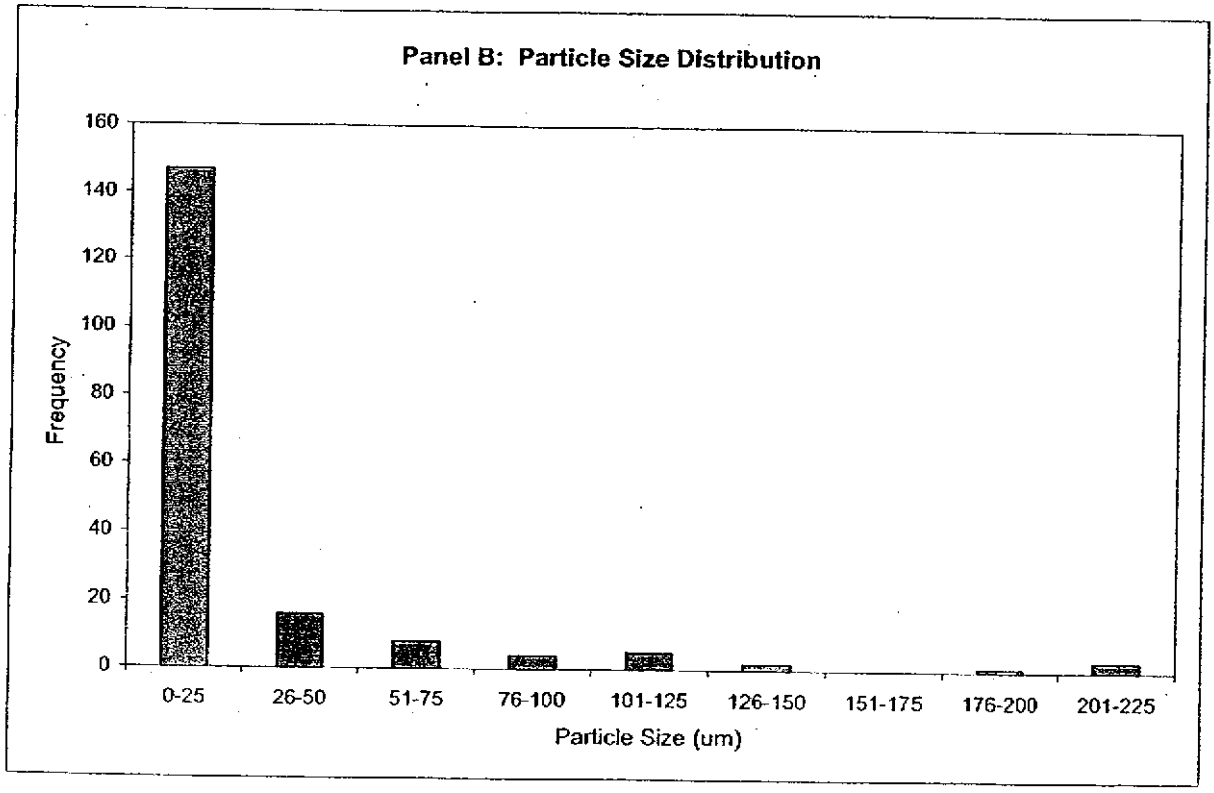
IVBA Results.xls (Summary and Graph)

APPENDIX A

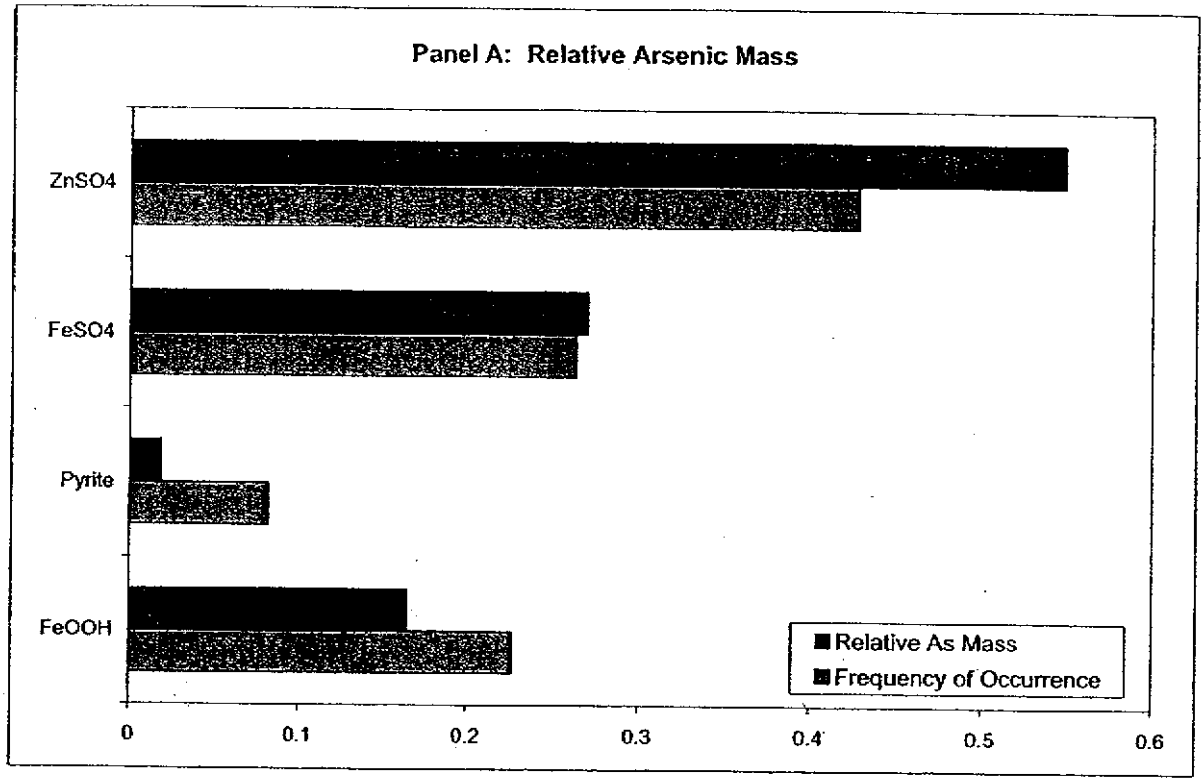
DETAILED ARSENIC SPECIATION RESULTS

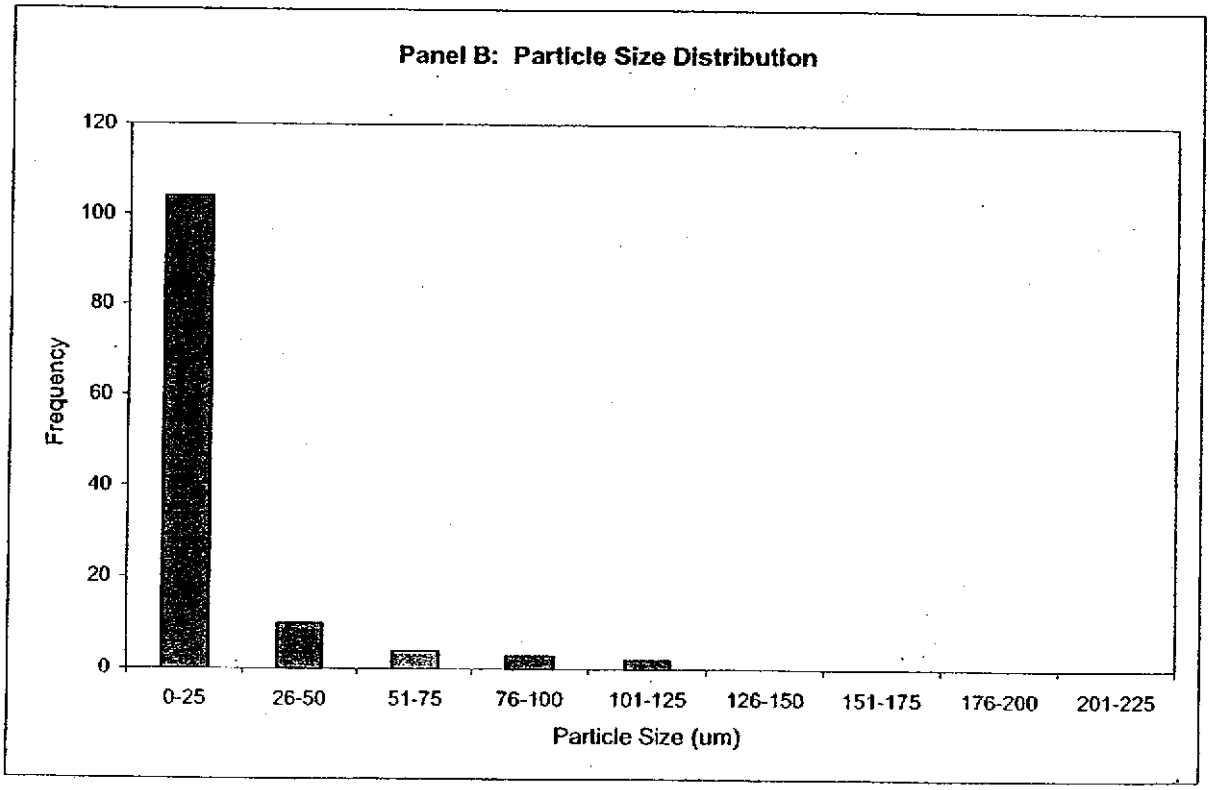
TEST MATERIAL 1 - SPECIATION AND PARTICLE SIZE DATA



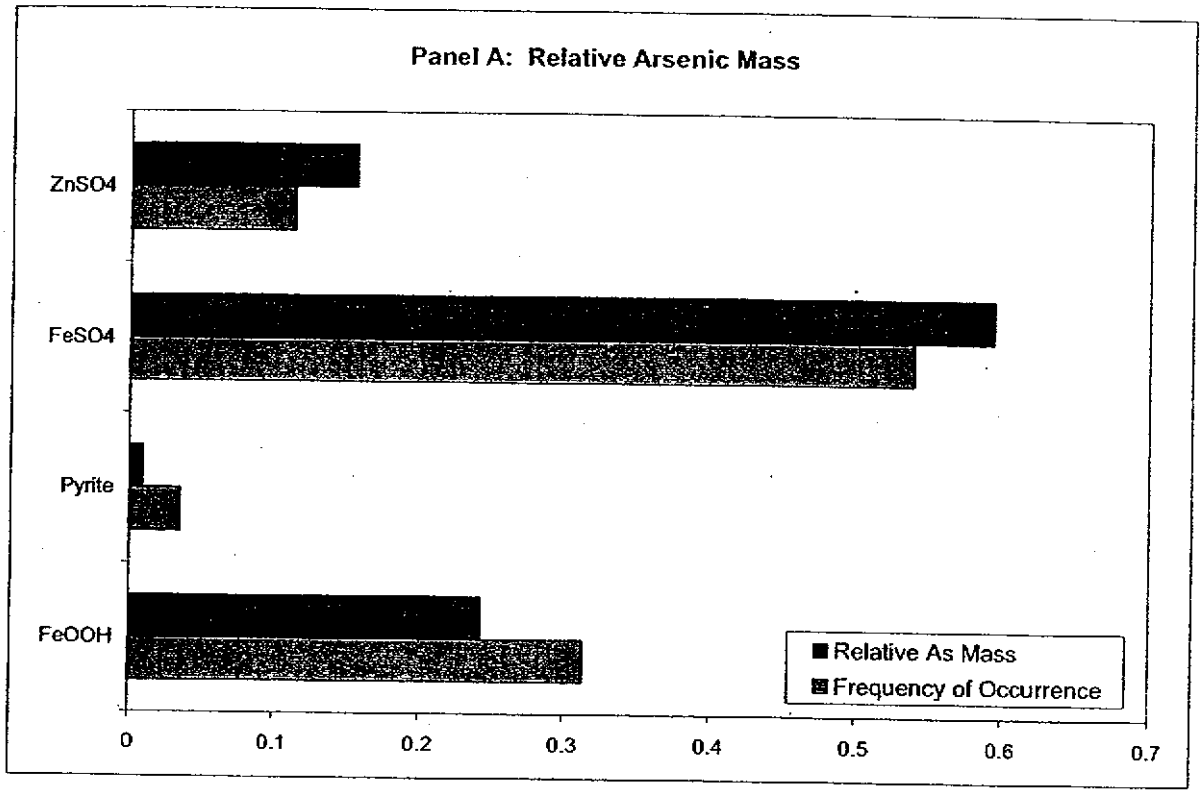


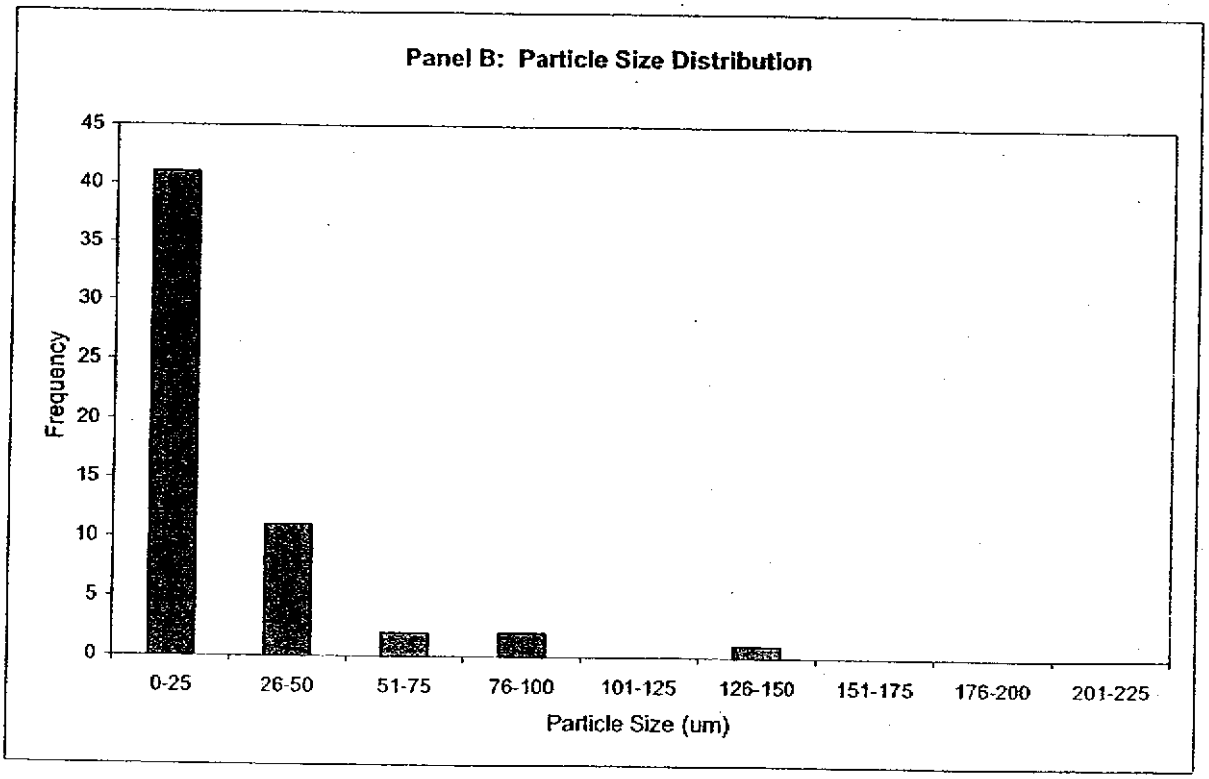
TEST MATERIAL 2 - SPECIATION AND PARTICLE SIZE DATA





TEST MATERIAL 3 - SPECIATION AND PARTICLE SIZE DATA





APPENDIX B

DETAILED RESULTS

TABLE B-1 SCHEDULE

Study Day	Day	Date	Dose Administration	Feed Special Diet	Weigh	Dose Prep	Cull Pigs/ Assign Dose Group	48 hr Urine Collection	Sacrifice
-8	Tuesday	8/27/02							
-7	Wednesday	8/28/02			X		X		
-6	Thursday	8/29/02							
-5	Friday	8/30/02							
-4	Saturday	8/31/02			X				
-3	Sunday	9/1/02							
-2	Monday	9/2/02		X					
-1	Tuesday	9/3/02	X	X	X	X			
0	Wednesday	9/4/02	X	X					
1	Thursday	9/5/02	X	X					
2	Friday	9/6/02	X	X	X	X			
3	Saturday	9/7/02	X	X					
4	Sunday	9/8/02	X	X					
5	Monday	9/9/02	X	X	X	X			
6	Tuesday	9/10/02	X	X					
7	Wednesday	9/11/02	X	X					
8	Thursday	9/12/02	X	X	X	X			
9	Friday	9/13/02	X	X					
10	Saturday	9/14/02	X	X					
11	Sunday	9/15/02	X	X	X				
12	Monday	9/16/02							X

Appendix B_detailed results.xls (schedule)

TABLE B-2 GROUP ASSIGNMENTS

Pig Number	Dose Group	Material Administered	Target Dose of Arsenic (ug/day)
324 338 349	1	Control	0
326 330 339 350	2	NaAs	300
310 316 322 340	3	NaAs	600
303 315 329 341	4	NaAs	900
301 318 344 347	5	TM1	300
309 327 343 346	6	TM1	600
306 308 317 331	7	TM1	900
304 311 314 321	8	TM2	300
307 313 325 332	9	TM2	600
328 337 342 348	10	TM2	900

TABLE B-3 BODY WEIGHTS AND ADMINISTERED DOSES, BY DAY

Body weights were measured on days -7, -4, -1, 2, 5, 8, and 11. Weights for other days are estimated, based on linear interpolation between measured values.

Group	Pig #	Day -7		Day -4		Day -1		Day 0		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9		Day 10		Day 11	
		BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day	BW kg	ugAs per day
1	324	10.15	0	10.25	0	11.15	0	11.48	0	11.82	0	12.15	0	12.57	0	12.98	0	13.40	0	13.75	0	14.10	0	14.45	0	14.87	0	15.28	0	15.70	0
1	338	8.9	0	9.46	0	10.9	0	11.0	0	11.2	0	11.3	0	11.7	0	12.1	0	12.45	0	12.8	0	13.1	0	13.46	0	14.1	0	14.8	0	15.4	0
1	349	10	0	9.45	0	10.75	0	11.1	0	11.4	0	11.75	0	12.1	0	12.5	0	12.85	0	13.3	0	13.8	0	14.2	0	14.8	0	15.0	0	15.4	0
2	326	11.05	300	11.2	300	11.9	300	12.3	300	12.8	300	13	300	13.3	300	13.7	300	14	300	14.4	300	14.8	300	15.25	300	15.8	300	16.4	300	16.9	300
2	330	9.85	300	10.3	300	11.35	300	11.5	300	11.7	300	11.85	300	12.3	300	12.7	300	13.15	300	13.5	300	13.9	300	14.25	300	14.8	300	15.4	300	16	300
2	339	8.2	300	9	300	9.85	300	10.3	300	10.8	300	11.2	300	11.5	300	11.8	300	12.15	300	12.5	300	13.0	300	13.45	300	14.0	300	14.5	300	15.05	300
2	350	10.55	300	10.45	300	11.25	300	11.6	300	12.0	300	12.3	300	12.7	300	13.1	300	13.45	300	13.9	300	14.4	300	14.9	300	15.4	300	15.9	300	16.35	300
3	310	11.55	600	11.65	600	12.55	600	12.8	600	13.0	600	13.2	600	13.5	600	13.9	600	14.2	600	14.6	600	15.5	600	16.1	600	16.5	600	16.9	600	17.3	600
3	316	9.65	600	10.2	600	11.7	600	12.0	600	12.3	600	12.55	600	12.9	600	13.3	600	13.65	600	14.0	600	14.4	600	14.75	600	15.4	600	16.1	600	16.7	600
3	322	10.45	600	10.95	600	11.8	600	12.2	600	12.5	600	12.9	600	13.3	600	13.8	600	14.2	600	14.9	600	15.6	600	16.25	600	16.9	600	17.6	600	18.3	600
3	340	7.8	600	8.2	600	9.05	600	9.3	600	9.6	600	9.85	600	10.2	600	10.5	600	10.85	600	11.2	600	11.5	600	11.75	600	12.2	600	12.7	600	13.2	600
4	303	11.35	900	11.25	900	12.5	900	12.70	900	12.9	900	13.1	900	13.8	900	14.1	900	14.65	900	16.2	900	15.9	900	16.4	900	16.9	900	17.4	900	17.85	900
4	315	10.45	900	10.75	900	11.95	900	12.2	900	12.5	900	12.75	900	13.2	900	13.7	900	14.2	900	14.6	900	14.9	900	15.25	900	15.8	900	16.4	900	16.95	900
4	329	11.05	900	11.6	900	12.9	900	13.4	900	13.8	900	14.25	900	14.7	900	15.2	900	15.6	900	16.0	900	16.5	900	16.9	900	17.4	900	18.0	900	18.5	900
4	341	8.85	900	9.95	900	11.45	900	11.7	900	12.0	900	12.3	900	12.7	900	13.0	900	13.4	900	14.0	900	14.6	900	15.15	900	15.9	900	16.7	900	17.45	900
5	301	13.1	257.802	13.45	257.802	14.85	257.802	15.0	258	15.3	258	15.6	257.802	16.2	258	16.9	258	17.5	257.802	18.2	258	18.8	258	19.45	257.802	20.0	258	20.6	258	21.1	257.802
5	318	11.2	257.802	11.3	257.802	12.35	257.802	12.6	258	12.7	258	12.9	257.802	13.4	258	13.9	258	14.45	257.802	15.0	258	15.6	258	16.1	257.802	16.6	258	17.2	258	17.7	257.802
5	344	10.6	257.802	10.25	257.802	11.1	257.802	11.3	258	11.5	258	11.75	257.802	12.3	258	12.8	258	13.3	257.802	13.8	258	14.2	258	14.7	257.802	15.2	258	15.6	258	16.1	257.802
5	347	8.35	257.802	8.4	257.802	9.45	257.802	9.8	258	10.1	258	10.4	257.802	10.8	258	11.3	258	11.7	257.802	12.0	258	12.4	258	12.7	257.802	13.0	258	13.6	258	14.35	257.802
6	309	8.7	515.604	9.9	515.604	10.6	515.604	11.0	516	11.3	516	11.6	515.604	11.8	516	12.2	516	12.5	515.604	13.1	516	13.7	516	14.3	515.604	14.7	516	15.1	516	15.5	515.604
6	327	9.85	515.604	10.15	515.604	11.25	515.604	11.5	516	11.9	516	12.15	515.604	12.5	516	13.1	516	13.6	515.604	14.2	516	14.8	516	15.4	515.604	15.7	516	15.9	516	16.2	515.604
6	343	9.4	515.604	9.1	515.604	10.1	515.604	10.4	516	10.7	516	10.95	515.604	11.4	516	11.8	516	12.15	515.604	12.6	516	13.0	516	[redacted]		13.6	516	13.8	516	[redacted]	
6	346	9.4	515.604	8.9	515.604	11	515.604	11.4	516	11.8	516	12.25	515.604	12.8	516	12.8	516	13.25	515.604	13.7	516	14.2	516	14.7	515.604	15.0	516	15.4	516	15.7	515.604
7	306	9.7	773.405	13.6	773.405	14.8	773.405	15.0	773	15.2	773	15.45	773.405	16.1	773	16.7	773	17.25	773.405	17.7	773	18.1	773	18.45	773.405	19.0	773	19.6	773	20.15	773.405
7	308	11.15	773.405	11.95	773.406	12.7	773.405	12.9	773	13.1	773	13.3	773.405	13.7	773	14.1	773	14.45	773.405	15.0	773	15.5	773	15.95	773.405	16.4	773	16.8	773	17.2	773.405
7	317	12.75	773.405	12.25	773.405	12.6	773.406	12.9	773	13.1	773	13.4	773.405	13.8	773	14.4	773	14.95	773.405	15.4	773	15.8	773	16.25	773.405	16.8	773	17.3	773	17.75	773.405
7	331	12.85	773.405	12.85	773.405	13.8	773.406	14.1	773	14.3	773	14.6	773.405	[redacted]		15.6	773	16.15	773.405	[redacted]		17.2	773	17.7	773.405	18.1	773	[redacted]		[redacted]	
8	304	10.1	269.655	10.6	269.655	12.1	269.655	12.4	270	12.7	270	13.06	269.655	13.4	270	13.7	270	14	269.655	14.3	270	14.7	270	15	269.655	15.7	270	16.3	270	17	269.655
8	311	11.4	269.655	11.95	269.655	12.75	269.655	13.0	270	13.3	270	13.6	269.655	13.9	270	14.4	270	14.8	269.655	15.3	270	15.8	270	16.3	269.655	16.9	270	17.6	270	18.2	269.655
8	314	10.45	269.655	10.8	269.655	11.5	269.655	11.9	270	12.3	270	12.69	269.655	13.0	270	13.4	270	13.8	269.655	14.5	270	15.1	270	15.8	269.655	16.2	270	16.8	270	16.9	269.655
8	321	11.95	269.655	12.1	269.655	12.45	269.655	12.8	270	13.1	270	13.4	269.655	13.9	270	14.3	270	14.78	269.655	15.2	270	15.7	270	16.15	269.656	16.7	270	17.2	270	17.65	269.655
9	307	13.7	539.31	13	539.31	13.6	539.31	14.0	539	14.3	539	14.65	539.31	14.9	539	15.2	539	[redacted]		15.8	539	[redacted]		16.45	539.31	16.9	539	17.4	539	17.85	539.31
9	313	12.55	539.31	12.9	539.31	13.4	539.31	[redacted]		14.2	539	[redacted]		15.0	539	15.4	539	15.85	539.31	16.1	539	16.4	539	16.8	539.31	17.4	539	18.2	539	19	539.31
9	325	11.45	539.31	11.7	539.31	12.25	539.31	12.5	539	12.7	539	12.95	539.31	13.4	539	13.9	539	14.35	539.31	[redacted]		[redacted]		[redacted]		[redacted]		17.4	539	17.95	539.31
9	332	11.95	539.31	11.5	539.31	12.4	539.31	12.7	539	12.9	539	13.2	539.31	13.7	539	14.2	539	14.65	539.31	15.2	539	15.7	539	16.15	539.31	16.4	539	16.7	539	16.9	539.31
10	328	11.05	808.966	11.25	808.966	12.1	808.966	12.5	809	12.8	809	13.15	808.966	13.8	809	14.1	809	14.5	808.966	15.1	809	15.7	809	[redacted]		16.5	809	17.3	809	17.75	808.966
10	337	8.5	808.966	9.1	808.966	9.75	808.966	[redacted]		10.4	809	[redacted]		11.2	809	[redacted]		12.1	808.966	[redacted]		13.0	809	[redacted]		[redacted]		[redacted]		[redacted]	
10	342	10.9	808.966	11.15	808.966	11.8	808.966	12.1	809	12.4	809	12.75	808.966	13.1	809	13.4	809	13.75	808.966	14.5	809	[redacted]		15.9	808.966	16.3	809	16.6	809	16.95	808.966
10	348	9.05	808.966	9.2	808.966	10.1	808.966	10.3	809	10.5	809	10.85	808.966	[redacted]		11.6	809	12.05	808.966	[redacted]		13.1	809	13.55	808.966	14.0	809	14.5	809	15	808.966

Missed Doses:

Day 0 - Pig 313 did not eat entire afternoon dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 0 - Pig 337 did not eat entire afternoon dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 2 - Pig 313 did not eat entire afternoon dose (ate approximately 90%). Daily dose adjusted to 95%.
Day 2 - Pig 337 did not eat entire morning dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 3 - Pig 331 did not eat entire afternoon dose (ate approximately 90%). Daily dose adjusted to 95%.
Day 3 - Pig 346 did not eat entire afternoon dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 4 - Pig 337 did not eat entire afternoon dose (ate approximately 90%). Daily dose adjusted to 95%.
Day 5 - Pig 307 did not eat entire morning dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 6 - Pig 331 did not eat entire morning dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 6 - Pig 325 did not eat entire afternoon dose (ate approximately 90%). Daily dose adjusted to 95%.
Day 6 - Pig 337 did not eat entire morning dose (ate approximately 90%). Daily dose adjusted to 95%.
Day 6 - Pig 348 did not eat entire afternoon dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 7 - Pig 307 did not eat entire afternoon dose (ate approximately 75%). Daily dose adjusted to 87.5%.
Day 7 - Pig 325 did not eat entire morning dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 7 - Pig 342 did not eat entire morning dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 8 - Pig 343 did not eat entire morning dose (ate approximately 90%). Daily dose adjusted to 95%.
Day 8 - Pig 325 did not eat entire morning dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 8 - Pig 328 did not eat entire morning dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 8 - Pig 337 did not eat entire afternoon dose (ate approximately 90%). Daily dose adjusted to 95%.
Day 9 - Pig 325 did not eat entire afternoon dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 9 - Pig 337 did not eat entire afternoon dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 10 - Pig 331 did not eat entire afternoon dose (ate approximately 95%). Daily dose adjusted to 97.5%.
Day 10 - Pig 337 did not eat entire morning or afternoon dose (ate approximately 70% and 95%, respectively). Daily dose adjusted to 82.5%.
Day 11 - Pig 343 did not eat entire afternoon dose (ate approximately 80%). Daily dose adjusted to 90%.
Day 11 - Pig 331 did not eat entire afternoon dose (ate approximately 80%). Daily dose adjusted to 90%.
Day 11 - Pig 337 did not eat entire afternoon dose (ate approximately 90%). Daily dose adjusted to 95%.

TABLE B-4 URINE VOLUMES - 48 HOUR COLLECTIONS

Units of Volume: mls

Group	Pig ID	Day		
		6-7 9/10-9/11	8-9 9/12-9/13	10-11 9/14-9/15
1	324	5400	6780	11620
	338	6960	7280	13800
	349	6100	4340	4460
2	326	6870	7640	14940
	330	3060	1900	3350
	339	19330	8320	18380
	350	12850	7640	10100
3	310	11150	3260	14060
	316	24060	50480	40840
	322	16940	8720	12400
	340	4840	3480	8100
4	303	10270	12800	13490
	315	12220	23700	16150
	329	21400	21620	26660
	341	5540	7260	8990
5	301	3360	2240	2020
	318	4960	4830	3440
	344	3440	4380	4010
	347	10700	10740	11690
6	309	18340	16790	19700
	327	6280	6360	9800
	343	7040	4480	9240
	346	22050	15820	16650
7	306	8220	8220	11620
	308	15500	11400	12200
	317	2520	2350	2150
	331	8180	8680	11180
8	304	5660	6600	4440
	311	23820	23920	29080
	314	6000	5250	4660
	321	10300	14600	7440
9	307	17000	21760	18000
	313	24830	16420	14660
	325	4360	4840	4050
	332	8910	6760	4290
10	328	15700	14470	21760
	337	3320	1400	3800
	342	14000	14200	33350
	348	3680	3840	4800

Volume measured by:	TE, CL, HH	HH, BL	HH,TN
Date:	9/12/02-9/13/02	9/14/02	9/16/02

TABLE B-5 URINE ANALYTICAL RESULTS

Tag Number	Pig Number	Group	Day	Material Administered	Target Dose (ug/d)	Qual	Arsenic Conc in Urine	DF	Units
R1-01-0194	324	1	6/7	Control	0	<	1	1	ng/mL
R1-01-0265	338	1	6/7	Control	0		1	1	ng/mL
R1-01-0173	349	1	6/7	Control	0		3	1	ng/mL
R1-01-0163	326	2	6/7	NaAs	300		83	1	ng/mL
R1-01-0200	330	2	6/7	NaAs	300		160	2	ng/mL
R1-01-0191	339	2	6/7	NaAs	300		29	1	ng/mL
R1-01-0228	350	2	6/7	NaAs	300		45	1	ng/mL
R1-01-0232	310	3	6/7	NaAs	600		110	2	ng/mL
R1-01-0199	316	3	6/7	NaAs	600		49	1	ng/mL
R1-01-0112	322	3	6/7	NaAs	600		73	1	ng/mL
R1-01-0250	340	3	6/7	NaAs	600		160	2	ng/mL
R1-01-0167	303	4	6/7	NaAs	900		170	2	ng/mL
R1-01-0220	315	4	6/7	NaAs	900		101	1	ng/mL
R1-01-0263	329	4	6/7	NaAs	900		70	1	ng/mL
R1-01-0233	341	4	6/7	NaAs	900		300	4	ng/mL
R1-01-0136	301	5	6/7	TM1	300		56	1	ng/mL
R1-01-0261	318	5	6/7	TM1	300		42	1	ng/mL
R1-01-0260	344	5	6/7	TM1	300		57	1	ng/mL
R1-01-0159	347	5	6/7	TM1	300		14	1	ng/mL
R1-01-0148	309	6	6/7	TM1	600		24	1	ng/mL
R1-01-0187	327	6	6/7	TM1	600		66	1	ng/mL
R1-01-0156	343	6	6/7	TM1	600		36	1	ng/mL
R1-01-0208	346	6	6/7	TM1	600		23	1	ng/mL
R1-01-0121	306	7	6/7	TM1	900		65	1	ng/mL
R1-01-0165	308	7	6/7	TM1	900		39	1	ng/mL
R1-01-0193	317	7	6/7	TM1	900		138	1	ng/mL
R1-01-0171	331	7	6/7	TM1	900		42	1	ng/mL
R1-01-0225	304	8	6/7	TM2	300		49	1	ng/mL
R1-01-0183	311	8	6/7	TM2	300		11	1	ng/mL
R1-01-0117	314	8	6/7	TM2	300		44	1	ng/mL
R1-01-0118	321	8	6/7	TM2	300		25	1	ng/mL
R1-01-0177	307	9	6/7	TM2	600		40	1	ng/mL
R1-01-0152	313	9	6/7	TM2	600		23	1	ng/mL
R1-01-0234	325	9	6/7	TM2	600		104	1	ng/mL
R1-01-0172	332	9	6/7	TM2	600		66	1	ng/mL
R1-01-0114	328	10	6/7	TM2	900		56	1	ng/mL
R1-01-0164	337	10	6/7	TM2	900		160	2	ng/mL
R1-01-0147	342	10	6/7	TM2	900		57	1	ng/mL
R1-01-0186	348	10	6/7	TM2	900		150	2	ng/mL
R1-01-0120	324	1	8/9	Control	0		2	1	ng/mL
R1-01-0237	338	1	8/9	Control	0		3	1	ng/mL
R1-01-0123	349	1	8/9	Control	0		3.6	1	ng/mL
R1-01-0139	326	2	8/9	NaAs	300		75	1	ng/mL
R1-01-0221	330	2	8/9	NaAs	300		270	5	ng/mL
R1-01-0107	339	2	8/9	NaAs	300		73	1	ng/mL
R1-01-0243	350	2	8/9	NaAs	300		71	1	ng/mL
R1-01-0189	310	3	8/9	NaAs	600		240	5	ng/mL
R1-01-0213	316	3	8/9	NaAs	600		24	1	ng/mL
R1-01-0111	322	3	8/9	NaAs	600		130	2	ng/mL

Tag Number	Pig Number	Group	Day	Material Administered	Target Dose (ug/d)	Q	Arsenic Conc in Urine	DL	Units
R1-01-0145	340	3	8/9	NaAs	600		240	5	ng/mL
R1-01-0132	303	4	8/9	NaAs	900		140	2	ng/mL
R1-01-0257	315	4	8/9	NaAs	900		70	1	ng/mL
R1-01-0240	329	4	8/9	NaAs	900		83	1	ng/mL
R1-01-0188	341	4	8/9	NaAs	900		240	5	ng/mL
R1-01-0215	301	5	8/9	TM1	300		77	1	ng/mL
R1-01-0133	318	5	8/9	TM1	300		48	1	ng/mL
R1-01-0218	344	5	8/9	TM1	300		39	1	ng/mL
R1-01-0255	347	5	8/9	TM1	300		19	1	ng/mL
R1-01-0138	309	6	8/9	TM1	600		29	1	ng/mL
R1-01-0170	327	6	8/9	TM1	600		65	1	ng/mL
R1-01-0251	343	6	8/9	TM1	600		60	1	ng/mL
R1-01-0141	346	6	8/9	TM1	600		24	1	ng/mL
R1-01-0127	306	7	8/9	TM1	900		66	1	ng/mL
R1-01-0258	308	7	8/9	TM1	900		51	1	ng/mL
R1-01-0205	317	7	8/9	TM1	900		160	5	ng/mL
R1-01-0161	331	7	8/9	TM1	900		58	1	ng/mL
R1-01-0242	304	8	8/9	TM2	300		39	1	ng/mL
R1-01-0253	311	8	8/9	TM2	300		11	1	ng/mL
R1-01-0166	314	8	8/9	TM2	300		52	1	ng/mL
R1-01-0262	321	8	8/9	TM2	300		19	1	ng/mL
R1-01-0105	307	9	8/9	TM2	600		28	1	ng/mL
R1-01-0134	313	9	8/9	TM2	600		32	1	ng/mL
R1-01-0185	325	9	8/9	TM2	600		98	1	ng/mL
R1-01-0113	332	9	8/9	TM2	600		80	1	ng/mL
R1-01-0144	328	10	8/9	TM2	900		63	1	ng/mL
R1-01-0101	337	10	8/9	TM2	900		440	10	ng/mL
R1-01-0210	342	10	8/9	TM2	900		54	1	ng/mL
R1-01-0196	348	10	8/9	TM2	900		190	5	ng/mL
R1-01-0202	324	1	10/11	Control	0	<	1	1	ng/mL
R1-01-0239	338	1	10/11	Control	0		1	1	ng/mL
R1-01-0142	349	1	10/11	Control	0		3	1	ng/mL
R1-01-0192	326	2	10/11	NaAs	300		40	1	ng/mL
R1-01-0224	330	2	10/11	NaAs	300		130	2	ng/mL
R1-01-0229	339	2	10/11	NaAs	300		33	1	ng/mL
R1-01-0108	350	2	10/11	NaAs	300		60	1	ng/mL
R1-01-0209	310	3	10/11	NaAs	600		74	1	ng/mL
R1-01-0207	316	3	10/11	NaAs	600		31	1	ng/mL
R1-01-0131	322	3	10/11	NaAs	600		100	1	ng/mL
R1-01-0219	340	3	10/11	NaAs	600		120	2	ng/mL
R1-01-0254	303	4	10/11	NaAs	900		96	1	ng/mL
R1-01-0125	315	4	10/11	NaAs	900		102	1	ng/mL
R1-01-0236	329	4	10/11	NaAs	900		68	1	ng/mL
R1-01-0264	341	4	10/11	NaAs	900		180	5	ng/mL
R1-01-0109	301	5	10/11	TM1	300		110	2	ng/mL
R1-01-0231	318	5	10/11	TM1	300		58	1	ng/mL
R1-01-0176	344	5	10/11	TM1	300		43	1	ng/mL
R1-01-0128	347	5	10/11	TM1	300		13	1	ng/mL
R1-01-0227	309	6	10/11	TM1	600		24	1	ng/mL
R1-01-0129	327	6	10/11	TM1	600		40	1	ng/mL
R1-01-0115	343	6	10/11	TM1	600		28	1	ng/mL
R1-01-0204	346	6	10/11	TM1	600		24	1	ng/mL

Tag Number	Pup Number	Group	Day	Maternal Administered	Target Dose (ug/d)	CF	Arsenic Conc in Urine	DL	Units
R1-01-0160	306	7	10/11	TM1	900		51	1	ng/mL
R1-01-0150	308	7	10/11	TM1	900		52	1	ng/mL
R1-01-0143	317	7	10/11	TM1	900		190	5	ng/mL
R1-01-0248	331	7	10/11	TM1	900		54	1	ng/mL
R1-01-0238	304	8	10/11	TM2	300		62	1	ng/mL
R1-01-0178	311	8	10/11	TM2	300		9.5	1	ng/mL
R1-01-0217	314	8	10/11	TM2	300		50	1	ng/mL
R1-01-0214	321	8	10/11	TM2	300		32	1	ng/mL
R1-01-0252	307	9	10/11	TM2	600		31	1	ng/mL
R1-01-0245	313	9	10/11	TM2	600		33	1	ng/mL
R1-01-0256	325	9	10/11	TM2	600		120	2	ng/mL
R1-01-0216	332	9	10/11	TM2	600		120	2	ng/mL
R1-01-0149	328	10	10/11	TM2	900		39	1	ng/mL
R1-01-0246	337	10	10/11	TM2	900		160	5	ng/mL
R1-01-0174	342	10	10/11	TM2	900		26	1	ng/mL
R1-01-0103	348	10	10/11	TM2	900		130	2	ng/mL
R1-01-0222	2340	3	6/7	NaAs	600		160	2	ng/mL
R1-01-0180	2306	7	6/7	TM1	900		61	1	ng/mL
R1-01-0244	2307	9	6/7	TM2	600		37	1	ng/mL
R1-01-0104	2329	4	8/9	NaAs	900		83	1	ng/mL
R1-01-0247	2346	6	8/9	TM1	600		28	1	ng/mL
R1-01-0110	2314	8	8/9	TM2	300		53	1	ng/mL
R1-01-0212	2330	2	10/11	NaAs	300		130	2	ng/mL
R1-01-0182	2344	5	10/11	TM1	300		44	1	ng/mL
R1-01-0151	2348	10	10/11	TM2	900		130	2	ng/mL
R1-01-0157	AsCtrl	PE		Control	0		3	1	ng/mL
R1-01-0206	AsCtrl	PE		Control	0		2	1	ng/mL
R1-01-0119	AsIA200	PE		Sodium arsenate	200		180	4	ng/mL
R1-01-0124	AsIA200	PE		Sodium arsenate	200		190	5	ng/mL
R1-01-0198	AsIA40	PE		Sodium arsenate	40		42	1	ng/mL
R1-01-0158	AsIA40	PE		Sodium arsenate	40		41	1	ng/mL
R1-01-0122	AsIB200	PE		Sodium arsenite	200		190	4	ng/mL
R1-01-0175	AsIB200	PE		Sodium arsenite	200		200	5	ng/mL
R1-01-0106	AsIB40	PE		Sodium arsenite	40		43	1	ng/mL
R1-01-0230	AsIB40	PE		Sodium arsenite	40		41	1	ng/mL
R1-01-0241	AsOA200	PE		MMA	200		200	4	ng/mL
R1-01-0130	AsOA200	PE		MMA	200		210	5	ng/mL
R1-01-0135	AsOA40	PE		MMA	40		43	1	ng/mL
R1-01-0169	AsOA40	PE		MMA	40		43	1	ng/mL
R1-01-0116	AsOB200	PE		DMA	200		200	4	ng/mL
R1-01-0203	AsOB200	PE		DMA	200		210	5	ng/mL
R1-01-0249	AsOB40	PE		DMA	40		44	1	ng/mL
R1-01-0154	AsOB40	PE		DMA	40		44	1	ng/mL

Appendix C.12

Lead Model Calculations

TABLE C.12a (RAGS D IEUBK LEAD WORKSHEET)
Site Name: Wells G&H Superfund Site OU2
Combined Site Evaluation
Receptor: Young Child (1 to 6 years) Exposure to Media as Described

1. Lead Screening Questions

Medium	Lead Concentration Used in Model Run		Basis for Lead Concentration Used For Model Run	Lead Screening Concentration		Basis for Lead Screening Level
	Value	Units		Value	Units	
Soil	112	mg/kg	Average Detected Value	400	mg/kg	Recommended Soil Screening Level
Sediment	184	mg/kg	Average Detected Value	400	mg/kg	Recommended Soil Screening Level

2. Lead Model Questions

Question	Response for Residential Lead Model
What lead model (version and date) was used?	IEUBK win32 Model 1.0 build 252
Where are the input values located in the risk assessment report?	Located in Appendix Appendix C.12.1
What range of media concentrations were used for the model?	Refer to Table C.12.1
What statistics were used to represent the exposure concentration terms and where are the data on concentrations in the risk assessment that support use of these statistics?	Arithmetic mean concentration from Appendix C-8
Was soil sample taken from top 2 cm? If not, why?	No
Was soil sample sieved? What size screen was used? If not sieved, provide rationale.	No
What was the point of exposure/location?	The point of exposure was the maximum mean concentration of lead in site media from all three properties.
Where are the output values located in the risk assessment report?	Located in Appendix C.12.3
Was the model run using default values only?	Yes
Was the default soil bioavailability used?	Yes
Was the default soil ingestion rate used?	Yes

1. Attach the IEUBK text output file and graph upon which the PRG was based as an appendix. For additional information, see www.epa.gov/superfund/programs/lead

Question	Response for Residential Lead Model
If non-default values were used, where are the rationale for the values located in the risk assessment report?	NA

3. Final Result

Medium	Result	Comment/PRG [1]
Soil	Input value of 112 mg/kg in soil results in 2.62% of young children above a blood lead level of 10 ug/dL. Geometric mean blood lead = 0.219 ug/dL. This exceeds the blood lead goal as described in the 1994 OSWER Directive of no more than 5% of children exceeding 10 ug/dL blood lead.	Based on site conditions, a PRG of calculation is not necessary.
Sediment	Input value of 184 mg/kg in soil results in 2.268% of young children above a blood lead level of 10 ug/dL. Geometric mean blood lead = 0.866 ug/dL. This exceeds the blood lead goal as described in the 1994 OSWER Directive of no more than 5% of children exceeding 10 ug/dL blood lead.	Based on site conditions, a PRG of calculation is not necessary.

1. Attach the IEUBK text output file and graph upon which the PRG was based as an appendix. For additional information, see www.epa.gov/superfund/programs/lead

C.12.1 Time Weigthed Average Concentration - IEUBK Parameter Inputs for Soil and Sediment

Future Recreational Child (1 - 6 yrs)

Soil

	Average Concentration (mg/kKg)		CT Exposure Frequency (days/yr)[1]		Time-weighted conc. (mg/Kg)	
Exposure Point	Current	Future	Current	Future	Current	Future
Aberjona (0-2 feet)		438		13		**112**
Aberjona (2-15 feet)		733		13		123
Aberjona Triangle (0-2 feet)		185		13		103
Whitney (0-2 feet)		302		13		107
Whitney (2-15 feet)		301		13		107
Murphy (0-2 feet)		317		13		108
Murphy (2-15 feet)		256		13		106

Sediment

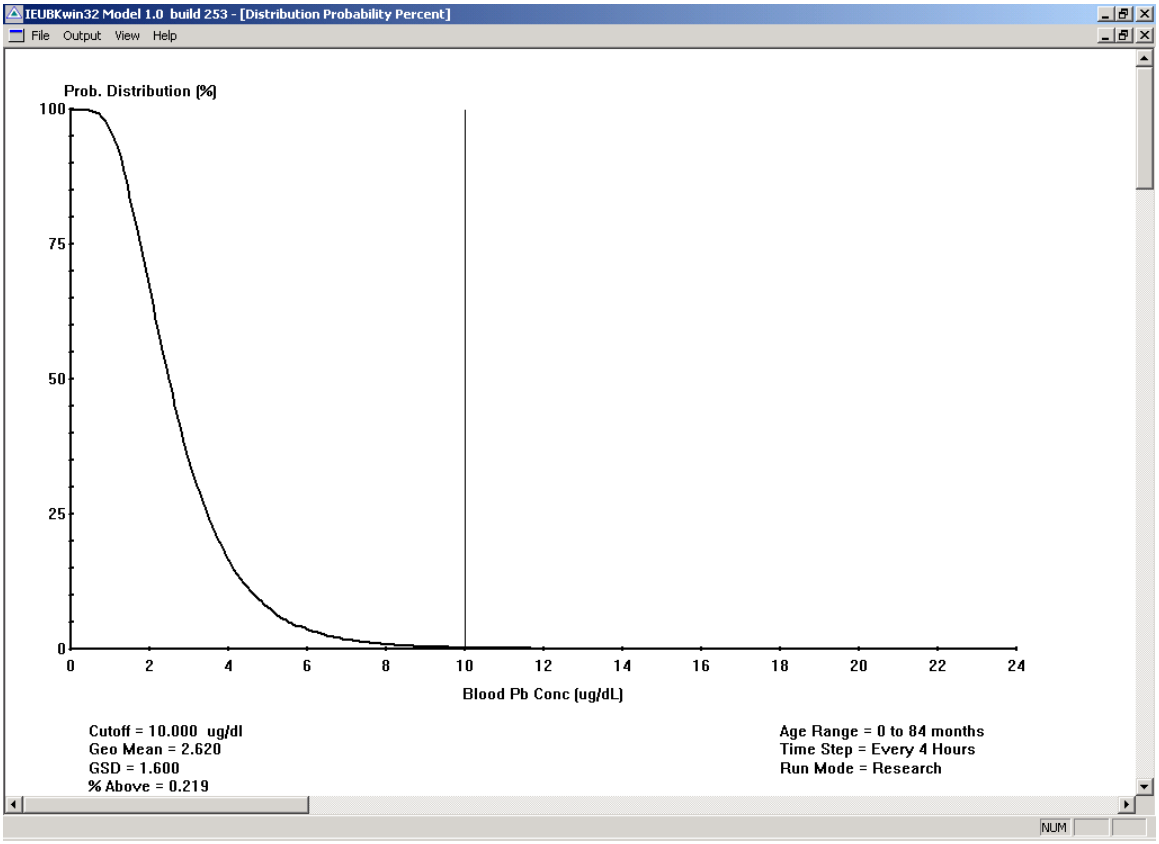
	Average Concentration (mg/kKg)		CT Exposure Frequency (days/yr)[1]		Time-weighted conc. (mg/Kg)	
Exposure Point	Current	Future	Current	Future	Current	Future
Murphy Wetlands		2450		13		**184**

Ground Water

	Average Concentration (ug/L)		CT Exposure Frequency (days/yr)[1]		Time-weighted conc. (mg/Kg)	
Exposure Point	Current	Future	Current	Future	Current	Future
Murphy Wetlands		85		350		**86**

Notes:
(1) Adjusted by fraction ingested term (50%)
(2) Time-weighted over one year using MADEP background value (MADEP, 2002) of 100 mg/Kg. If average concentration less than 100 mg/Kg
The average concentration is used.
Time weighted concentration = (((Average Conc. * Exposure Freq.) + (Bkgd. Conc. * (365-Exposure Freq.))/365)

C.12.2 IEUBK Child Recreational Graph for Soil



C.12.3 Soil Test Output - LEAD MODEL FOR WINDOWS Version 1.0 Build 252

Future Child Recreational - Soil

==========
Model Version: 1.0 Build 252
User Name: TRC Environmental
Date: 1-Aug-03
Site Name: Worst Case Evaluation for Aberjona, Whitney and Murphy Properties
Operable Unit:
Run Mode: Research
==========
The time step used in this model run: 1 - Every 4 Hours (6 times a day).

****** Air ******

Indoor Air Pb Concentration: 30.000 percent of outdoor.
Other Air Parameters:

Age	Time Outdoors (hours)	Ventilation Rate (m^3/day)	Lung Absorption (%)	Outdoor Air Pb Conc (ug Pb/m^3)
.5-1	1.000	2.000	32.000	0.100
1-2	2.000	3.000	32.000	0.100
2-3	3.000	5.000	32.000	0.100
3-4	4.000	5.000	32.000	0.100
4-5	4.000	5.000	32.000	0.100
5-6	4.000	7.000	32.000	0.100
6-7	4.000	7.000	32.000	0.100

****** Diet ******

Age	Diet Intake(ug/day)
.5-1	5.530
1-2	5.780
2-3	6.490
3-4	6.240
4-5	6.010
5-6	6.340
6-7	7.000

****** Drinking Water ******

Water Consumption:

Age	Water (L/day)
.5-1	0.200
1-2	0.500
2-3	0.520
3-4	0.530
4-5	0.550
5-6	0.580
6-7	0.590

Drinking Water Concentration: 4.000 ug Pb/L

****** Soil & Dust ******

C.12.3 Soil Test Output - LEAD MODEL FOR WINDOWS Version 1.0 Build 252

Multiple Source Analysis Used
Average multiple source concentration: 138.800 ug/g

Mass fraction of outdoor soil to indoor dust conversion factor: 0.700
Outdoor airborne lead to indoor household dust lead concentration: 100.000
Use alternate indoor dust Pb sources? No

Age	Soil (ug Pb/g)	House Dust (ug Pb/g)
.5-1	184.000	138.800
1-2	184.000	138.800
2-3	184.000	138.800
3-4	184.000	138.800
4-5	184.000	138.800
5-6	184.000	138.800
6-7	184.000	138.800

****** Alternate Intake ******

Age	Alternate (ug Pb/day)
.5-1	0.000
1-2	0.000
2-3	0.000
3-4	0.000
4-5	0.000
5-6	0.000
6-7	0.000

****** Maternal Contribution: Infant Model ******

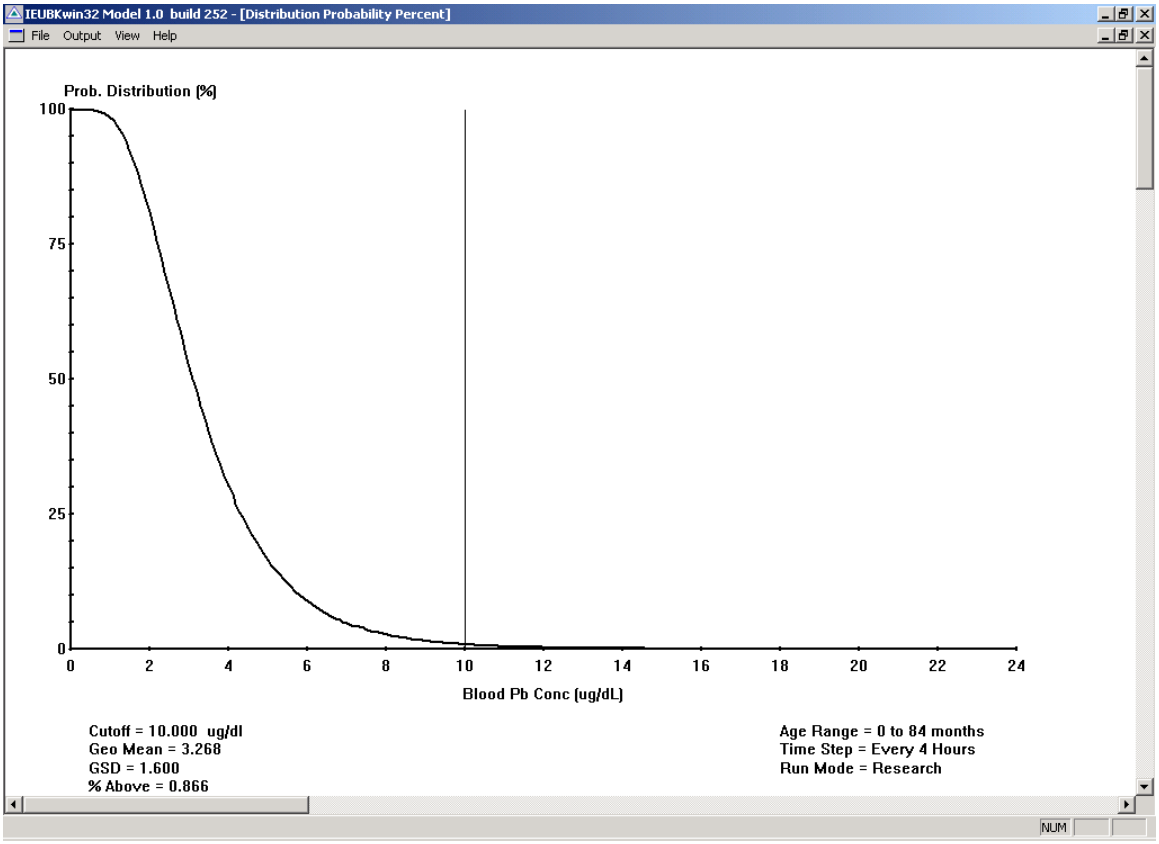
Maternal Blood Concentration: 2.500 ug Pb/dL

****
CALCULATED BLOOD LEAD AND LEAD UPTAKES:
****

Year	Air (ug/dL)	Diet (ug/day)	Alternate (ug/day)	Water (ug/day)
.5-1	0.021	2.562	0.000	0.371
1-2	0.034	2.658	0.000	0.920
2-3	0.062	3.012	0.000	0.965
3-4	0.067	2.928	0.000	0.995
4-5	0.067	2.869	0.000	1.050
5-6	0.093	3.045	0.000	1.114
6-7	0.093	3.371	0.000	1.137

Year	Soil+Dust (ug/day)	Total (ug/day)	Blood (ug/dL)
.5-1	3.759	6.713	3.6
1-2	5.928	9.540	4.0
2-3	5.983	10.023	3.7
3-4	6.049	10.038	3.5
4-5	4.558	8.543	3.0
5-6	4.127	8.380	2.6
6-7	3.909	8.510	2.4

C.12.4 IEUBK Child Recreational Graph for Sediment



C.12.5 Sediment Test Output - LEAD MODEL FOR WINDOWS Version 1.0 Build 252

Future Child Recreational - Sediment

==========
Model Version: 1.0 Build 252
User Name: TRC Environmental
Date: 1-Aug-03
Site Name: Murphy Property - Wetland Sediments
Operable Unit:
Run Mode: Research
==========
The time step used in this model run: 1 - Every 4 Hours (6 times a day).

****** Air ******

Indoor Air Pb Concentration: 30.000 percent of outdoor.
Other Air Parameters:

Age	Time Outdoors (hours)	Ventilation Rate (m^3/day)	Lung Absorption (%)	Outdoor Air Pb Conc (ug Pb/m^3)
.5-1	1.000	2.000	32.000	0.100
1-2	2.000	3.000	32.000	0.100
2-3	3.000	5.000	32.000	0.100
3-4	4.000	5.000	32.000	0.100
4-5	4.000	5.000	32.000	0.100
5-6	4.000	7.000	32.000	0.100
6-7	4.000	7.000	32.000	0.100

****** Diet ******

Age	Diet Intake(ug/day)
.5-1	5.530
1-2	5.780
2-3	6.490
3-4	6.240
4-5	6.010
5-6	6.340
6-7	7.000

****** Drinking Water ******

Water Consumption:

Age	Water (L/day)
.5-1	0.200
1-2	0.500
2-3	0.520
3-4	0.530
4-5	0.550
5-6	0.580
6-7	0.590

Drinking Water Concentration: 4.000 ug Pb/L
****** Soil & Dust ******

C.12.5 Sediment Test Output - LEAD MODEL FOR WINDOWS Version 1.0 Build 252

Multiple Source Analysis Used
Average multiple source concentration: 1725.000 ug/g

Mass fraction of outdoor soil to indoor dust conversion factor: 0.700
Outdoor airborne lead to indoor household dust lead concentration: 100.000
Use alternate indoor dust Pb sources? No

Age	Soil (ug Pb/g)	House Dust (ug Pb/g)
.5-1	2450.000	1725.000
1-2	2450.000	1725.000
2-3	2450.000	1725.000
3-4	2450.000	1725.000
4-5	2450.000	1725.000
5-6	2450.000	1725.000
6-7	2450.000	1725.000

****** Alternate Intake ******

Age	Alternate (ug Pb/day)
.5-1	0.000
1-2	0.000
2-3	0.000
3-4	0.000
4-5	0.000
5-6	0.000
6-7	0.000

****** Maternal Contribution: Infant Model ******

Maternal Blood Concentration: 2.500 ug Pb/dL

****
CALCULATED BLOOD LEAD AND LEAD UPTAKES:
****

Year	Air (ug/dL)	Diet (ug/day)	Alternate (ug/day)	Water (ug/day)
.5-1	0.021	1.799	0.000	0.260
1-2	0.034	1.771	0.000	0.613
2-3	0.062	2.090	0.000	0.670
3-4	0.067	2.106	0.000	0.716
4-5	0.067	2.265	0.000	0.829
5-6	0.093	2.500	0.000	0.915
6-7	0.093	2.830	0.000	0.954

Year	Soil+Dust (ug/day)	Total (ug/day)	Blood (ug/dL)
.5-1	34.036	36.116	18.4
1-2	50.918	53.336	21.1
2-3	53.517	56.340	20.1
3-4	56.086	58.975	19.7
4-5	46.393	49.554	16.9
5-6	43.684	47.193	14.6
6-7	42.301	46.179	13.0

TABLE C.12b (RAGS D ADULT LEAD WORKSHEET)
Site Name: Wells G&H Superfund Site OU2
Combined Site Evaluation
Receptor: Adult Non-Resident – Future Adult Recreational, Exposure to Media as Described

1. Lead Screening Questions

Medium	Lead Concentration used in Model Run		Basis for Lead Concentration Used For Model Run	Lead Screening Concentration		Basis for Lead Screening Level
	Value	Units		Value	Units	
Soil	123	mg/kg	Average Detected Value	750	mg/kg	Recommended Soil Screening Level
Sediment	184	mg/kg	Average Detected Value	750	mg/kg	Recommended Soil Screening Level

2. Lead Model Questions

Question	Response
What lead model was used? Provide reference and version	Adult Model associated with EPA-540-R-03-001
If the EPA Adult Lead Model (ALM) was not used provide rationale for model selected.	N/A
Where are the input values located in the risk assessment report?	Located in Appendix C.12, Table C.12-8
What statistics were used to represent the exposure concentration terms and where are the data on concentrations in the risk assessment that support use of these statistics?	Arithmetic mean concentration from Appendix C-8
What was the point of exposure and location?	The point of exposure was the maximum mean concentration of lead in site media from all three properties for the 0-2 and 2-15 foot intervals.
Where are the output values located in the risk assessment report?	Located in Appendix C.12, Table C.12-8
What GSD value was used? If this is outside the recommended range of 1.8-2.1), provide rationale in Appendix <Y>.	1.8
What baseline blood lead concentration (PbB_0) value was used? If this is outside the default range of 1.7 to 2.2 provide rationale in Appendix <Y>	2.0
Was the default exposure frequency (EF; 219 days/year) used?	No
Was the default BKSF used (0.4 ug/dL per ug/day) used?	Yes
Was the default absorption fraction (AF; 0.12) used?	Yes
Was the default soil ingestion rate (IR; 50 mg/day) used?	Yes
If non-default values were used for any of the parameters listed above, where are the rationale for the values located in the risk assessment report?	Located in Appendix C.12, Tables C.12-7 and C.12-8

1. Attach the ALM spreadsheet output file upon which the Risk Based Remediation Goal (RBRG) was based and description of rationale for parameters used. For additional information, see www.epa.gov/superfund/programs/lead

TABLE C.12c (RAGS D ADULT LEAD WORKSHEET)
Site Name: Wells G&H Superfund Site OU2
Combined Site Evaluation
Receptor: Adult Non-Resident – Commercial Worker, Exposure to Media as Described

1. Lead Screening Questions

Medium	Lead Concentration used in Model Run		Basis for Lead Concentration Used For Model Run	Lead Screening Concentration		Basis for Lead Screening Level
	Value	Units		Value	Units	
Soil	216	mg/kg	Average Detected Value	750	mg/kg	Recommended Soil Screening Level

2. Lead Model Questions

Question	Response
What lead model was used? Provide reference and version	Adult Model associated with EPA-540-R-03-001
If the EPA Adult Lead Model (ALM) was not used provide rationale for model selected.	N/A
Where are the input values located in the risk assessment report?	Located in Appendix C.12, Table C.12-8
What statistics were used to represent the exposure concentration terms and where are the data on concentrations in the risk assessment that support use of these statistics?	Arithmetic mean concentration from Appendix C-8
What was the point of exposure and location?	The point of exposure was the maximum mean concentration of lead in site media from all three properties for the 0-2 interval.
Where are the output values located in the risk assessment report?	Located in Appendix C.12, Table C.12-8
What GSD value was used? If this is outside the recommended range of 1.8-2.1), provide rationale in Appendix <Y>.	1.8
What baseline blood lead concentration (PbB_0) value was used? If this is outside the default range of 1.7 to 2.2 provide rationale in Appendix <Y>	2.0
Was the default exposure frequency (EF; 219 days/year) used?	No
Was the default BKSF used (0.4 ug/dL per ug/day) used?	Yes
Was the default absorption fraction (AF; 0.12) used?	Yes
Was the default soil ingestion rate (IR; 50 mg/day) used?	Yes
If non-default values were used for any of the parameters listed above, where are the rationale for the values located in the risk assessment report?	Located in Appendix C.12, Table C.12-9

3. Final Result

Medium	Result	Comment/RBRG [1]
Soil	Input value of 123 ppm in soil results in 0.3% of receptors above a blood lead level of 10 ug/d and geometric mean blood lead = 2.0 ug/dL. This exceeds the blood lead goal as described in the 1994 OSWER Directive of no more than 5% of children (fetuses of exposed women) exceeding 10 ug/dL blood lead.	Based on site conditions, a RBRG calculation is not necessary.

1. Attach the ALM spreadsheet output file upon which the Risk Based Remediation Goal (RBRG) was based and description of rationale for parameters used. For additional information, see www.epa.gov/superfund/programs/lead

3. Final Result

Medium	Result	Comment/RBRG [1]
Soil	Input value of 123 ppm in soil results in 0.2% of receptors above a blood lead level of 10 ug/d and geometric mean blood lead = 2.0 ug/dL. This exceeds the blood lead goal as described in the 1994 OSWER Directive of no more than 5% of children (fetuses of exposed women) exceeding 10 ug/dL blood lead.	Based on site conditions, a RBRG calculation is not necessary.
Sediment	Input value of 184 ppm in soil results in 0.2% of receptors above a blood lead level of 10 ug/d and geometric mean blood lead = 2.0 ug/dL. This exceeds the blood lead goal as described in the 1994 OSWER Directive of no more than 5% of children (fetuses of exposed women) exceeding 10 ug/dL blood lead.	Based on site conditions, a RBRG calculation is not necessary.

1. Attach the ALM spreadsheet output file upon which the Risk Based Remediation Goal (RBRG) was based and description of rationale for parameters used. For additional information, see www.epa.gov/superfund/programs/lead

TABLE C.12d (RAGS D ADULT LEAD WORKSHEET)
Site Name: Wells G&H Superfund Site OU2
Combined Site Evaluation
Receptor: Adult Non-Resident – Construction Worker, Exposure to Media as Described

1. Lead Screening Questions

Medium	Lead Concentration used in Model Run		Basis for Lead Concentration Used For Model Run	Lead Screening Concentration		Basis for Lead Screening Level
	Value	Units		Value	Units	
Soil	169	mg/kg	Average Detected Value	750	mg/kg	Recommended Soil Screening Level

2. Lead Model Questions

Question	Response
What lead model was used? Provide reference and version	Adult Model associated with EPA-540-R-03-001
If the EPA Adult Lead Model (ALM) was not used provide rationale for model selected.	N/A
Where are the input values located in the risk assessment report?	Located in Appendix C.12, Table C.12-8
What statistics were used to represent the exposure concentration terms and where are the data on concentrations in the risk assessment that support use of these statistics?	Arithmetic mean concentration from Appendix C-8
What was the point of exposure and location?	The point of exposure was the maximum mean concentration of lead in site media from all three properties for the 0-2 and 2-15 foot intervals.
Where are the output values located in the risk assessment report?	Located in Appendix C.12, Table C.12-8
What GSD value was used? If this is outside the recommended range of 1.8-2.1), provide rationale in Appendix <Y>.	1.8
What baseline blood lead concentration (PbB_0) value was used? If this is outside the default range of 1.7 to 2.2 provide rationale in Appendix <Y>	2.0
Was the default exposure frequency (EF; 219 days/year) used?	No
Was the default BKSF used (0.4 ug/dL per ug/day) used?	Yes
Was the default absorption fraction (AF; 0.12) used?	Yes
Was the default soil ingestion rate (IR; 50 mg/day) used?	Yes
If non-default values were used for any of the parameters listed above, where are the rationale for the values located in the risk assessment report?	Located in Appendix C.12, Table C.12-10

3. Final Result

Medium	Result	Comment/RBRG [1]
Soil	Input value of 123 ppm in soil results in 0.3% of receptors above a blood lead level of 10 ug/d and geometric mean blood lead = 2.0 ug/dL. This exceeds the blood lead goal as described in the 1994 OSWER Directive of no more than 5% of children (fetuses of exposed women) exceeding 10 ug/dL blood lead.	Based on site conditions, a RBRG calculation is not necessary.

1. Attach the ALM spreadsheet output file upon which the Risk Based Remediation Goal (RBRG) was based and description of rationale for parameters used. For additional information, see www.epa.gov/superfund/programs/lead

TABLE C.12e (RAGS D ADULT LEAD WORKSHEET)
Site Name: Wells G&H Superfund Site OU2
Combined Site Evaluation
Receptor: Adult Non-Resident – Future Older Child Trespasser, Exposure to Media as Described

1. Lead Screening Questions

Medium	Lead Concentration used in Model Run		Basis for Lead Concentration Used For Model Run	Lead Screening Concentration		Basis for Lead Screening Level
	Value	Units		Value	Units	
Soil	112	mg/kg	Average Detected Value	750	mg/kg	Recommended Soil Screening Level
Sediment	184	mg/kg	Average Detected Value	750	mg/kg	Recommended Soil Screening Level

2. Lead Model Questions

Question	Response
What lead model was used? Provide reference and version	Adult Model associated with EPA-540-R-03-001
If the EPA Adult Lead Model (ALM) was not used provide rationale for model selected.	N/A
Where are the input values located in the risk assessment report?	Located in Appendix C.12, Table C.12-8
What statistics were used to represent the exposure concentration terms and where are the data on concentrations in the risk assessment that support use of these statistics?	Arithmetic mean concentration from Appendix C-8
What was the point of exposure and location?	The point of exposure was the maximum mean concentration of lead in site media from all three properties for the 0-2 and 2-15 foot intervals.
Where are the output values located in the risk assessment report?	Located in Appendix C.12, Table C.12-8
What GSD value was used? If this is outside the recommended range of 1.8-2.1), provide rationale in Appendix <Y>.	1.8
What baseline blood lead concentration (PbB_0) value was used? If this is outside the default range of 1.7 to 2.2 provide rationale in Appendix <Y>	2.0
Was the default exposure frequency (EF; 219 days/year) used?	No
Was the default BKSF used (0.4 ug/dL per ug/day) used?	Yes
Was the default absorption fraction (AF; 0.12) used?	Yes
Was the default soil ingestion rate (IR; 50 mg/day) used?	Yes
If non-default values were used for any of the parameters listed above, where are the rationale for the values located in the risk assessment report?	Located in Appendix C.12, Tables C.12-11 and C.12-12

1. Attach the ALM spreadsheet output file upon which the Risk Based Remediation Goal (RBRG) was based and description of rationale for parameters used. For additional information, see www.epa.gov/superfund/programs/lead

3. Final Result

Medium	Result	Comment/RBRG [1]
Soil	Input value of 123 ppm in soil results in 0.2% of receptors above a blood lead level of 10 ug/d and geometric mean blood lead = 2.0 ug/dL. This exceeds the blood lead goal as described in the 1994 OSWER Directive of no more than 5% of children (fetuses of exposed women) exceeding 10 ug/dL blood lead.	Based on site conditions, a RBRG calculation is not necessary.
Sediment	Input value of 184 ppm in soil results in 0.2% of receptors above a blood lead level of 10 ug/d and geometric mean blood lead = 2.0 ug/dL. This exceeds the blood lead goal as described in the 1994 OSWER Directive of no more than 5% of children (fetuses of exposed women) exceeding 10 ug/dL blood lead.	Based on site conditions, a RBRG calculation is not necessary.

1. Attach the ALM spreadsheet output file upon which the Risk Based Remediation Goal (RBRG) was based and description of rationale for parameters used. For additional information, see www.epa.gov/superfund/programs/lead

Table C.12-6 Time Weigthed Average Concentration - Adult Parameter Inputs for Soil and Sediment

Future Trespasser

Soil

	Average Concentration (mg/kKg)		CT Exposure Frequency (days/yr)[1]		Time-weighted conc. (mg/Kg)	
Exposure Point	Current	Future	Current	Future	Current	Future
Aberjona (0-2 feet)	438	438	13	13	**112**	**112**
Aberjona Triangle (0-2 feet)	185	185	13	13	103	103
Whitney (0-2 feet)	302	302	13	13	107	107
Murphy (0-2 feet)	317	317	13	13	108	108

Sediment

	Average Concentration (mg/kKg)		CT Exposure Frequency (days/yr)[1]		Time-weighted conc. (mg/Kg)	
Exposure Point	Current	Future	Current	Future	Current	Future
Murphy Wetlands	2450	2450	13	13	**184**	**184**

Current/Future Commercial Worker

Soil

	Average Concentration (mg/kKg)		CT Exposure Frequency (days/yr)		Time-weighted conc. (mg/Kg)	
Exposure Point	Current	Future	Current	Future	Current	Future
Aberjona (0-2 feet)	438	438	125	125	**216**	**216**
Aberjona Triangle (0-2 feet)	185	185	125	125	129	129
Whitney (0-2 feet)	302	302	125	125	169	169
Murphy (0-2 feet)	317	317	125	125	174	174

Table C.12-6 Time Weigthed Average Concentration - Adult Parameter Inputs for Soil and Sediment

Future Recreational (Adult)

Soil

	Average Concentration (mg/kKg)		CT Exposure Frequency (days/yr)[1]		Time-weighted conc. (mg/Kg)	
Exposure Point	Current	Future	Current	Future	Current	Future
Aberjona (0-2 feet)	--	438	--	13	--	112
Aberjona (2-15 feet)	--	733	--	13	--	**123**
Aberjona Triangle (0-2 feet)	--	185	--	13	--	103
Whitney (0-2 feet)	--	302	--	13	--	107
Whitney (2-15 feet)	--	301	--	13	--	107
Murphy (0-2 feet)	--	317	--	13	--	108
Murphy (2-15 feet)	--	256	--	13	--	106

Sediment

	Average Concentration (mg/kKg)		CT Exposure Frequency (days/yr)[1]		Time-weighted conc. (mg/Kg)	
Exposure Point	Current	Future	Current	Future	Current	Future
Murphy Wetlands	--	2450	--	13	--	**184**

Future Construction Worker

Soil

	Average Concentration (mg/kKg)		CT Exposure Frequency (days/yr)		Time-weighted conc. (mg/Kg)	
Exposure Point	Current	Future	Current	Future	Current	Future
Aberjona (0-2 feet)	--	438	--	40	--	137
Aberjona (2-15 feet)	--	733	--	40	--	**169**
Aberjona Triangle (0-2 feet)	--	185	--	40	--	109
Whitney (0-2 feet)	--	302	--	40	--	122
Whitney (2-15 feet)	--	301	--	40	--	122
Murphy (0-2 feet)	--	317	--	40	--	124
Murphy (2-15 feet)	--	256	--	40	--	117

Notes:
Exposure to sediment only evaluated for Future Older Child Trespasser and Future Adult Recreational User
(1) Adjusted by fraction ingested term (50%)
(2) Time-weighted over one year using MADEP background value (MADEP, 2002) of 100 mg/Kg. If average concentration less than 100 mg/Kg The average concentration is used.
Time weighted concentration = (((Average Conc. * Exposure Freq.) + (Bkgd. Conc. * (365-Exposure Freq.))/365)

Table C.12.7 - Calculations of Blood Lead Concentrations (PbBs) - Adult Recreational Worst Case Evaluation for Aberjona, Whitney and Murphy Properties - Soil (0 - 2 feet and 2-15 feet)

Calculations of Blood Lead Concentrations (PbBs)

U.S. EPA Technical Review Workgroup for Lead, Adult Lead Committee

Version date 05/19/03

Exposure Variable	PbB Equation[1] 1*	PbB Equation[1] 2**	Description of Exposure Variable	Units	Values for Non-Residential Exposure Scenario - Construction: Using Equation 1 GSDi = Hom	Using Equation 1 GSDi = Het	Using Equation 2 GSDi = Hom	Using Equation 2 GSDi = Het
PbS	X	X	Soil lead concentration	ug/g or ppm	123		123	
$R_{fetal/maternal}$	X	X	Fetal/maternal PbB ratio	--	0.9		0.9	
BKSF	X	X	Biokinetic Slope Factor	ug/dL per ug/day	0.4		0.4	
GSD_i	X	X	Geometric standard deviation PbB	--	1.8		1.8	
PbB_0	X	X	Baseline PbB	ug/dL	2.0		2.0	
IR_S	X		Soil ingestion rate (including soil-derived indoor dust)	g/day	0.050		--	
IR_{S+D}		X	Total ingestion rate of outdoor soil and indoor dust	g/day	--		0.050	
W_S		X	Weighting factor; fraction of IR_{S+D} ingested as outdoor soil	--	--		1.0	
K_{SD}		X	Mass fraction of soil in dust	--	--		0.7	
$AF_{S, D}$	X	X	Absorption fraction (same for soil and dust)	--	0.12		0.12	
$EF_{S, D}$	X	X	Exposure frequency (same for soil and dust)	days/yr	26		26	
$AT_{S, D}$	X	X	Averaging time (same for soil and dust)	days/yr	365		365	
PbB_{adult}	**PbB of adult worker, geometric mean**			**ug/dL**	**2.0**		**2.0**	
$PbB_{fetal, 0.95}$	**95th percentile PbB among fetuses of adult workers**			**ug/dL**	**4.8**		**4.8**	
PbB_t	**Target PbB level of concern (e.g., 10 ug/dL)**			**ug/dL**	**10.0**		**10.0**	
$P(PbB_{fetal} > PbB_t)$	**Probability that fetal PbB > PbB_t, assuming lognormal distribution**			**%**	**0.2%**		**0.2%**	

[1] Equation 1 does not apportion exposure between soil and dust ingestion (excludes W_S, K_{SD}).
When $IR_S = IR_{S+D}$ and $W_S = 1.0$, the equations yield the same $PbB_{fetal,0.95}$.

***Equation 1, based on Eq. 1, 2 in USEPA (1996).**

PbB_{adult} =	$(PbS*BKSF*IR_{S+D}*AF_{S,D}*EF_S/AT_{S,D}) + PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

****Equation 2, alternate approach based on Eq. 1, 2, and A-19 in USEPA (1996).**

PbB_{adult} =	$PbS*BKSF*([(IR_{S+D})*AF_S*EF_S*W_S]+[K_{SD}*(IR_{S+D})*(1-W_S)*AF_D*EF_D])/365+PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

Source: U.S. EPA (1996). Recommendations of the Technical Review Workgroup for Lead for an Interim Approach to Assessing Risks Associated with Adult Exposures to Lead in Soil

Table C.12.8 - Calculations of Blood Lead Concentrations (PbBs) - Adult Recreational Worst Case Evaluation for Aberjona, Whitney and Murphy Properties - Sediment

Calculations of Blood Lead Concentrations (PbBs)

U.S. EPA Technical Review Workgroup for Lead, Adult Lead Committee

Version date 05/19/03

Exposure Variable	PbB Equation[1] 1*	PbB Equation[1] 2**	Description of Exposure Variable	Units	Values for Non-Residential Exposure Scenario - Construction: Using Equation 1 GSDi = Hom	Using Equation 1 GSDi = Het	Using Equation 2 GSDi = Hom	Using Equation 2 GSDi = Het
PbS	X	X	Soil lead concentration	ug/g or ppm	184		184	
$R_{fetal/maternal}$	X	X	Fetal/maternal PbB ratio	--	0.9		0.9	
BKSF	X	X	Biokinetic Slope Factor	ug/dL per ug/day	0.4		0.4	
GSD_i	X	X	Geometric standard deviation PbB	--	1.8		1.8	
PbB_0	X	X	Baseline PbB	ug/dL	2.0		2.0	
IR_S	X		Soil ingestion rate (including soil-derived indoor dust)	g/day	0.050		--	
IR_{S+D}		X	Total ingestion rate of outdoor soil and indoor dust	g/day	--		0.050	
W_S		X	Weighting factor; fraction of IR_{S+D} ingested as outdoor soil	--	--		1.0	
K_{SD}		X	Mass fraction of soil in dust	--	--		0.7	
$AF_{S, D}$	X	X	Absorption fraction (same for soil and dust)	--	0.12		0.12	
$EF_{S, D}$	X	X	Exposure frequency (same for soil and dust)	days/yr	26		26	
$AT_{S, D}$	X	X	Averaging time (same for soil and dust)	days/yr	365		365	
PbB_{adult}	**PbB of adult worker, geometric mean**			**ug/dL**	**2.0**		**2.0**	
$PbB_{fetal, 0.95}$	**95th percentile PbB among fetuses of adult workers**			**ug/dL**	**4.8**		**4.8**	
PbB_t	**Target PbB level of concern (e.g., 10 ug/dL)**			**ug/dL**	**10.0**		**10.0**	
$P(PbB_{fetal} > PbB_t)$	**Probability that fetal PbB > PbB_t, assuming lognormal distribution**			**%**	**0.2%**		**0.2%**	

[1] Equation 1 does not apportion exposure between soil and dust ingestion (excludes W_S, K_{SD}).
When $IR_S = IR_{S+D}$ and $W_S = 1.0$, the equations yield the same $PbB_{fetal,0.95}$.

***Equation 1, based on Eq. 1, 2 in USEPA (1996).**

PbB_{adult} =	$(PbS*BKSF*IR_{S+D}*AF_{S,D}*EF_S/AT_{S,D}) + PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

****Equation 2, alternate approach based on Eq. 1, 2, and A-19 in USEPA (1996).**

PbB_{adult} =	$PbS*BKSF*([(IR_{S+D})*AF_S*EF_S*W_S]+[K_{SD}*(IR_{S+D})*(1-W_S)*AF_D*EF_D])/365+PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

Table C.12-9 - Calculations of Blood Lead Concentrations (PbBs) - Adult Commercial Worker Worst Case Evaluation for Aberjona, Whitney, and Murphy Properties - Soil (0 - 2 feet)

Calculations of Blood Lead Concentrations (PbBs)

U.S. EPA Technical Review Workgroup for Lead, Adult Lead Committee

Version date 05/19/03

Exposure Variable	PbB Equation[1] 1*	PbB Equation[1] 2**	Description of Exposure Variable	Units	Values for Non-Residential Exposure Scenario - Construction: Using Equation 1 GSDi = Hom	Using Equation 1 GSDi = Het	Using Equation 2 GSDi = Hom	Using Equation 2 GSDi = Het
PbS	X	X	Soil lead concentration	ug/g or ppm	216		216	
$R_{fetal/maternal}$	X	X	Fetal/maternal PbB ratio	--	0.9		0.9	
BKSF	X	X	Biokinetic Slope Factor	ug/dL per ug/day	0.4		0.4	
GSD_i	X	X	Geometric standard deviation PbB	--	1.8		1.8	
PbB_0	X	X	Baseline PbB	ug/dL	2.0		2.0	
IR_S	X		Soil ingestion rate (including soil-derived indoor dust)	g/day	0.050		--	
IR_{S+D}		X	Total ingestion rate of outdoor soil and indoor dust	g/day	--		0.050	
W_S		X	Weighting factor; fraction of IR_{S+D} ingested as outdoor soil	--	--		1.0	
K_{SD}		X	Mass fraction of soil in dust	--	--		0.7	
$AF_{S, D}$	X	X	Absorption fraction (same for soil and dust)	--	0.12		0.12	
$EF_{S, D}$	X	X	Exposure frequency (same for soil and dust)	days/yr	125		125	
$AT_{S, D}$	X	X	Averaging time (same for soil and dust)	days/yr	365		365	
PbB_{adult}	**PbB of adult worker, geometric mean**			**ug/dL**	**2.2**		**2.2**	
$PbB_{fetal, 0.95}$	**95th percentile PbB among fetuses of adult workers**			**ug/dL**	**5.2**		**5.2**	
PbB_t	**Target PbB level of concern (e.g., 10 ug/dL)**			**ug/dL**	**10.0**		**10.0**	
$P(PbB_{fetal} > PbB_t)$	**Probability that fetal PbB > PbB_t, assuming lognormal distribution**			**%**	**0.3%**		**0.3%**	

[1] Equation 1 does not apportion exposure between soil and dust ingestion (excludes W_S, K_{SD}).
When $IR_S = IR_{S+D}$ and $W_S = 1.0$, the equations yield the same $PbB_{fetal,0.95}$.

***Equation 1, based on Eq. 1, 2 in USEPA (1996).**

PbB_{adult} =	$(PbS*BKSF*IR_{S+D}*AF_{S,D}*EF_S/AT_{S,D}) + PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

****Equation 2, alternate approach based on Eq. 1, 2, and A-19 in USEPA (1996).**

PbB_{adult} =	$PbS*BKSF*([(IR_{S+D})*AF_S*EF_S*W_S]+[K_{SD}*(IR_{S+D})*(1-W_S)*AF_D*EF_D])/365+PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

Source: U.S. EPA (1996). Recommendations of the Technical Review Workgroup for Lead for an Interim Approach to Assessing Risks Associated with Adult Exposures to Lead in Soil

Table C.12-10 - Calculations of Blood Lead Concentrations (PbBs) - Construction Worker Worst Case Evaluation for Aberjona, Whitney and Murphy Properties - Soil (0 - 2 feet and 2-15 feet)

Calculations of Blood Lead Concentrations (PbBs)

U.S. EPA Technical Review Workgroup for Lead, Adult Lead Committee

Version date 05/19/03

Exposure Variable	PbB Equation[1] 1*	PbB Equation[1] 2**	Description of Exposure Variable	Units	Values for Non-Residential Exposure Scenario - Construction: Using Equation 1 GSDi = Hom	Using Equation 1 GSDi = Het	Using Equation 2 GSDi = Hom	Using Equation 2 GSDi = Het
PbS	X	X	Soil lead concentration	ug/g or ppm	169		169	
$R_{fetal/maternal}$	X	X	Fetal/maternal PbB ratio	--	0.9		0.9	
BKSF	X	X	Biokinetic Slope Factor	ug/dL per ug/day	0.4		0.4	
GSD_i	X	X	Geometric standard deviation PbB	--	1.8		1.8	
PbB_0	X	X	Baseline PbB	ug/dL	2.0		2.0	
IR_S	X		Soil ingestion rate (including soil-derived indoor dust)	g/day	0.200		--	
IR_{S+D}		X	Total ingestion rate of outdoor soil and indoor dust	g/day	--		0.050	
W_S		X	Weighting factor; fraction of IR_{S+D} ingested as outdoor soil	--	--		1.0	
K_{SD}		X	Mass fraction of soil in dust	--	--		0.7	
$AF_{S, D}$	X	X	Absorption fraction (same for soil and dust)	--	0.12		0.12	
$EF_{S, D}$	X	X	Exposure frequency (same for soil and dust)	days/yr	40		40	
$AT_{S, D}$	X	X	Averaging time (same for soil and dust)	days/yr	365		365	
PbB_{adult}	**PbB of adult worker, geometric mean**			**ug/dL**	**2.2**		**2.0**	
$PbB_{fetal, 0.95}$	**95th percentile PbB among fetuses of adult workers**			**ug/dL**	**5.2**		**4.8**	
PbB_t	**Target PbB level of concern (e.g., 10 ug/dL)**			**ug/dL**	**10.0**		**10.0**	
$P(PbB_{fetal} > PbB_t)$	**Probability that fetal PbB > PbB_t, assuming lognormal distribution**			**%**	**0.3%**		**0.2%**	

[1] Equation 1 does not apportion exposure between soil and dust ingestion (excludes W_S, K_{SD}).
When $IR_S = IR_{S+D}$ and $W_S = 1.0$, the equations yield the same $PbB_{fetal,0.95}$.

***Equation 1, based on Eq. 1, 2 in USEPA (1996).**

PbB_{adult} =	$(PbS*BKSF*IR_{S+D}*AF_{S,D}*EF_S/AT_{S,D}) + PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

****Equation 2, alternate approach based on Eq. 1, 2, and A-19 in USEPA (1996).**

PbB_{adult} =	$PbS*BKSF*([(IR_{S+D})*AF_S*EF_S*W_S]+[K_{SD}*(IR_{S+D})*(1-W_S)*AF_D*EF_D])/365+PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

Source: U.S. EPA (1996). Recommendations of the Technical Review Workgroup for Lead for an Interim Approach to Assessing Risks Associated with Adult Exposures to Lead in Soil

Table C.12-11 - Calculations of Blood Lead Concentrations (PbBs) - Older Child Current/Future Trespasser Worst Case for Aberjona, Whitney and Murphy Properties - Soil (0 - 2 feet)

Calculations of Blood Lead Concentrations (PbBs)

U.S. EPA Technical Review Workgroup for Lead, Adult Lead Committee

Version date 05/19/03

Exposure Variable	PbB Equation[1] 1*	PbB Equation[1] 2**	Description of Exposure Variable	Units	Values for Non-Residential Exposure Scenario - Construction: Using Equation 1 GSDi = Hom	Using Equation 1 GSDi = Het	Using Equation 2 GSDi = Hom	Using Equation 2 GSDi = Het
PbS	X	X	Soil lead concentration	ug/g or ppm	112		112	
$R_{fetal/maternal}$	X	X	Fetal/maternal PbB ratio	--	0.9		0.9	
BKSF	X	X	Biokinetic Slope Factor	ug/dL per ug/day	0.4		0.4	
GSD_i	X	X	Geometric standard deviation PbB	--	1.8		1.8	
PbB_0	X	X	Baseline PbB	ug/dL	2.0		2.0	
IR_S	X		Soil ingestion rate (including soil-derived indoor dust)	g/day	0.050		--	
IR_{S+D}		X	Total ingestion rate of outdoor soil and indoor dust	g/day	--		0.050	
W_S		X	Weighting factor; fraction of IR_{S+D} ingested as outdoor soil	--	--		1.0	
K_{SD}		X	Mass fraction of soil in dust	--	--		0.7	
$AF_{S, D}$	X	X	Absorption fraction (same for soil and dust)	--	0.12		0.12	
$EF_{S, D}$	X	X	Exposure frequency (same for soil and dust)	days/yr	26		26	
$AT_{S, D}$	X	X	Averaging time (same for soil and dust)	days/yr	365		365	
PbB_{adult}	**PbB of adult worker, geometric mean**			**ug/dL**	**2.0**		**2.0**	
$PbB_{fetal, 0.95}$	**95th percentile PbB among fetuses of adult workers**			**ug/dL**	**4.8**		**4.8**	
PbB_t	**Target PbB level of concern (e.g., 10 ug/dL)**			**ug/dL**	**10.0**		**10.0**	
$P(PbB_{fetal} > PbB_t)$	**Probability that fetal PbB > PbB_t, assuming lognormal distribution**			**%**	**0.2%**		**0.2%**	

[1] Equation 1 does not apportion exposure between soil and dust ingestion (excludes W_S, K_{SD}).
When $IR_S = IR_{S+D}$ and $W_S = 1.0$, the equations yield the same $PbB_{fetal,0.95}$.

***Equation 1, based on Eq. 1, 2 in USEPA (1996).**

PbB_{adult} =	$(PbS*BKSF*IR_{S+D}*AF_{S,D}*EF_S/AT_{S,D}) + PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

****Equation 2, alternate approach based on Eq. 1, 2, and A-19 in USEPA (1996).**

PbB_{adult} =	$PbS*BKSF*([(IR_{S+D})*AF_S*EF_S*W_S]+[K_{SD}*(IR_{S+D})*(1-W_S)*AF_D*EF_D])/365+PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

Source: U.S. EPA (1996). Recommendations of the Technical Review Workgroup for Lead for an Interim Approach to Assessing Risks Associated with Adult Exposures to Lead in Soil

Table C.12-12 - Calculations of Blood Lead Concentrations (PbBs) - Older Child Current/Future Trespasser Worst Case for Aberjona, Whitney and Murphy Properties - Sediment

Calculations of Blood Lead Concentrations (PbBs)

U.S. EPA Technical Review Workgroup for Lead, Adult Lead Committee

Version date 05/19/03

Exposure Variable	PbB Equation[1] 1*	PbB Equation[1] 2**	Description of Exposure Variable	Units	Values for Non-Residential Exposure Scenario - Construction: Using Equation 1 GSDi = Hom	Using Equation 1 GSDi = Het	Using Equation 2 GSDi = Hom	Using Equation 2 GSDi = Het
PbS	X	X	Soil lead concentration	ug/g or ppm	184		184	
$R_{fetal/maternal}$	X	X	Fetal/maternal PbB ratio	--	0.9		0.9	
BKSF	X	X	Biokinetic Slope Factor	ug/dL per ug/day	0.4		0.4	
GSD_i	X	X	Geometric standard deviation PbB	--	1.8		1.8	
PbB_0	X	X	Baseline PbB	ug/dL	2.0		2.0	
IR_S	X		Soil ingestion rate (including soil-derived indoor dust)	g/day	0.050		--	
IR_{S+D}		X	Total ingestion rate of outdoor soil and indoor dust	g/day	--		0.050	
W_S		X	Weighting factor; fraction of IR_{S+D} ingested as outdoor soil	--	--		1.0	
K_{SD}		X	Mass fraction of soil in dust	--	--		0.7	
$AF_{S, D}$	X	X	Absorption fraction (same for soil and dust)	--	0.12		0.12	
$EF_{S, D}$	X	X	Exposure frequency (same for soil and dust)	days/yr	26		26	
$AT_{S, D}$	X	X	Averaging time (same for soil and dust)	days/yr	365		365	
PbB_{adult}	**PbB of adult worker, geometric mean**			**ug/dL**	**2.0**		**2.0**	
$PbB_{fetal, 0.95}$	**95th percentile PbB among fetuses of adult workers**			**ug/dL**	**4.8**		**4.8**	
PbB_t	**Target PbB level of concern (e.g., 10 ug/dL)**			**ug/dL**	**10.0**		**10.0**	
$P(PbB_{fetal} > PbB_t)$	**Probability that fetal PbB > PbB_t, assuming lognormal distribution**			**%**	**0.2%**		**0.2%**	

[1] Equation 1 does not apportion exposure between soil and dust ingestion (excludes W_S, K_{SD}).
When $IR_S = IR_{S+D}$ and $W_S = 1.0$, the equations yield the same $PbB_{fetal,0.95}$.

***Equation 1, based on Eq. 1, 2 in USEPA (1996).**

PbB_{adult} =	$(PbS*BKSF*IR_{S+D}*AF_{S,D}*EF_S/AT_{S,D}) + PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

****Equation 2, alternate approach based on Eq. 1, 2, and A-19 in USEPA (1996).**

PbB_{adult} =	$PbS*BKSF*([(IR_{S+D})*AF_S*EF_S*W_S]+[K_{SD}*(IR_{S+D})*(1-W_S)*AF_D*EF_D])/365+PbB_0$
$PbB_{fetal, 0.95}$ =	$PbB_{adult} * (GSD_i^{1.645} * R)$

Source: U.S. EPA (1996). Recommendations of the Technical Review Workgroup for Lead for an Interim Approach to Assessing Risks Associated with Adult Exposures to Lead in Soil