Appendix A: Background Information for Jet Fuels

Jet fuels are complex mixtures of hydrocarbons produced by distillation of petroleum crude oil. Most jet fuels (e.g., JP-5, JP-7, JP-8) are middle distillates similar in composition to kerosene and containing primarily C_9–C_{16} hydrocarbons (approximately 80% aliphatic and 20% aromatic). JP-4 is a "wide-cut" fuel that is a blend of kerosene with lower boiling naphtha streams, like those used to produce gasoline, and therefore, containing a greater range of hydrocarbons (C_4–C_{16}). Although the composition of JP-4 is notably different from the kerosene-type fuels, and minor differences exist also among the latter, obvious differences in toxicity have not been reported in the published literature. Therefore, these fuels are discussed together below.

A.1 Toxicokinetics

Absorption following inhalation exposure to jet fuels and related substances can be inferred from the occurrence of systemic health effects in humans and research animals exposed by inhalation (ATSDR 1995a, 1995b, 1998). In addition, studies have demonstrated that a mixture of aliphatic hydrocarbons mostly in the C_{10}–C_{12} range (white spirit) was readily absorbed through the lungs in humans, that individual alkanes and cycloalkanes in the range of C_6–C_{10} were absorbed in rats exposed by inhalation, and that isopropylbenzene (cumene), which is representative of the aromatic C_9–C_{16} fraction, had a pulmonary retention percentage of approximately 50% in human volunteers (ATSDR 1999). Data on oral absorption of jet fuels and related substances are limited, but suggest that these substances are absorbed from the gastrointestinal tract (ATSDR 1995a, 1995b, 1998). Gastrointestinal absorption of aliphatic hydrocarbons is inversely proportional to length of the carbon chain; absorption is approximately 60% for C_{14} hydrocarbons (ATSDR 1999). Aromatic hydrocarbons in this size range are well absorbed from the gut when administered at low doses: 80–90% of ingested 2-methylnaphthalene and isopropylbenzene was recovered in the urine (ATSDR 1999). Oral exposure can also result in the fuels being aspirated into the lungs, leading to respiratory effects (ATSDR 1995a, 1998). Systemic health effects have been reported following dermal application of JP-5, kerosene, and several aromatic compounds of the appropriate size (isopropylbenzene, naphthalene, monomethylnaphthalenes), indicating that these substances are absorbed through the skin (ATSDR 1995a, 1995b, 1998, 1999). McDougal et al. (2000) studied skin absorption and penetration of JP-8 and its components in an *in vitro* system using rat skin. These researchers found that total flux of hydrocarbons across the skin was a relatively slow 20.3 μg/cm^2/hour. A total of 13 individual components were found to penetrate the skin, with fluxes ranging from a high of 51.5 μg/cm^2/hour for diethylene glycol monomethyl ether (an additive) to 0.334 μg/cm^2/hour for

tridecane. In general, aromatic compounds penetrated skin more rapidly than aliphatics. Six compounds, all aliphatic, were absorbed into the skin; concentrations ranged from 0.055 µg/g skin (tetradecane) to 0.266 µg/g skin (undecane) after 3.5 hours.

Limited data suggest that jet fuels and related substances are widely distributed throughout the body after being absorbed (ATSDR 1995a, 1995b, 1998, 1999). Studies with white spirit (C_{10}–C_{12} aliphatic) and individual aliphatic hydrocarbons in the C_6–C_{10} range showed that these chemicals can accumulate in fat (ATSDR 1999). Following gastrointestinal absorption, the larger molecular weight aliphatics are transported primarily by the lymphatic system, while the smaller ones are transported by both the lymph and the blood. There is no information available on metabolism of jet fuels and related substances (ATSDR 1995a, 1995b, 1998), but data on C_9–C_{16} hydrocarbons suggest that metabolism of aliphatics in this range (primarily cytochrome P-450 mediated oxidation to fatty acids and alcohols) is slow, while the aromatics are metabolized faster (oxidation of alkyl site and/or ring, sometimes with formation of reactive intermediates, and conjugation with glutathione, glucuronic acid, or glycine) (ATSDR 1999). Data on elimination of jet fuels and related substances are not available (ATSDR 1995a, 1995b, 1998). It is noteworthy, however, that white spirit (C_{10}–C_{12} aliphatic) is only slowly eliminated from the fat, while aromatics in this size range are excreted rapidly as metabolites in the urine (ATSDR 1999).

A.2 Health Effects

Jet fuels can produce central nervous system impairment in humans by all routes of exposure, characterized by effects such as fatigue, coordination and concentration difficulties, headache, intoxication, anorexia, depressed mood, lack of initiative, dizziness, sleep disturbances, changes in posture, and reduced sensorimotor speed (ATSDR 1995b, 1998, 1999). Unconsciousness, coma, and convulsions have been observed after ingestion of kerosene by children. Similar symptoms of central nervous system depression have been observed in animal studies. Jet fuels and related substances can also produce respiratory, gastrointestinal, dermal, and ocular irritation in humans and animals (ATSDR 1995b, 1998, 1999). Respiratory effects may occur as a result of inhalation of jet fuel vapor, but in humans, have been more commonly and severely associated with aspiration into the lungs following oral exposure. Gastrointestinal effects have been noted after both inhalation and oral exposure. Dermal effects are usually a result of direct skin contact with the fuel, but have also been reported after oral exposure. Eye irritation has been reported as a consequence of exposure to jet fuel vapor in humans, although studies of direct ocular contact in animals have been negative.

Animal studies have also identified the liver, kidney, and immune system as targets for jet fuel toxicity. The liver is a sensitive and commonly affected endpoint in animal studies. MRLs for JP-4, JP-5, JP-7, and JP-8 are all based on liver effects (ATSDR 1995b, 1998). Observed effects in the liver include degenerative fatty change, hepatocellular necrosis, and hepatic inflammation. Hepatotoxicity was also indicated by increases in serum enzyme activities. In the kidney, animal studies have shown that jet fuels produce hyaline droplet nephropathy, which is unique to male rats and not predictive of renal effects in humans. Jet fuels and kerosine have also been found to produce immunosuppression (suppressed hypersensitivity reactions to antigens, suppressed ability of splenic T-cells to respond to mitogens, decreased number of viable immune cells, decreased immune organ weights) by inhalation and dermal exposure, while also being weak dermal sensitizers themselves (ATSDR 1998; Stoica et al. 2001; Ullrich 1999). A developmental toxicity study of JP-8 found decreased fetal body weight associated with oral exposure during gestation, but only at doses that also produced significant decreases in maternal weight gain (ATSDR 1998). Data regarding reproductive toxicity are not available. Genotoxicity testing has been fairly extensive, and the results have been overwhelmingly negative (ATSDR 1995b, 1998). Skin painting studies with jet fuels and kerosene have produced evidence suggesting that chronic dermal application of these substances can produce skin tumors (ATSDR 1995b, 1998, 1999; Rosenthal et al. 2001). Dermal tumorigenesis or tumor promotion by these substances may be related to their ability to produce skin irritation and dermal cell toxicity (Rosenthal et al. 2001). Data regarding internal cancers in humans and animals are equivocal.

A.3 Mechanisms of Action

Central nervous system depression, as observed for jet fuels, is an effect common to many organic solvents. It is generally thought to occur when the lipophilic parent compound partitions into the nerve cell membranes and disrupts function of membrane proteins by disturbing their lipid environment or by directly altering protein conformation (ATSDR 1999). Oxidative metabolism of the parent compounds reduces their lipophilicity and counteracts their central nervous system depressive effects. The hydrocarbon parent compounds in jet fuels are also thought to be responsible for the respiratory irritation and pneumonitis that can result from inhalation or aspiration of these fuels. It has been hypothesized that the parent hydrocarbons interact with nerve cell membranes, resulting in bronchoconstriction, and dissolve into membranes of the lung parenchyma, resulting in hemorrhagic exudation of proteins, cells, and fibrin into the alveoli (ATSDR 1999). *In vitro* experiments have shown that JP-8 induces apoptotic cell death in rat lung epithelial cells, apparently by damaging mitochondria in the cells (Stoica et al. 2001). JP-8 also induced apoptosis in immune system cells (U-937 human monocytic cells, Jurkat T-cell leukemia cells,

primary mouse thymocytes) *in vitro* (Stoica et al. 2001). In contrast, JP-8 produced necrotic cell death in primary and immortalized human keratinocytes and primary mouse skin fibroblasts in culture and when applied topically to immortalized human keratinocytes grafted onto nude mice (Rosenthal et al. 2001). While the central nervous system and irritant effects of jet fuels are apparently due to the parent hydrocarbons, effects on the liver and kidney are probably due to formation of reactive intermediates and metabolites during oxidative metabolism, and to subsequent binding of these reactive species to cellular macromolecules.

A.4 Health Guidelines

ATSDR (1995a) derived an intermediate-duration inhalation MRL of 9 mg/m^3 for JP-4 based on a lowest-observed-adverse-effect level (LOAEL) of 500 mg/m^3 for hepatotoxicity (hepatocellular fatty change) in female mice in a 90-day continuous exposure study, a human equivalent dose conversion factor of 5.7, and an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability). ATSDR (1995b) also derived a chronic inhalation MRL of 0.3 mg/m^3 for JP-7 based on a LOAEL of 150 mg/m^3 for hepatic inflammation in female mice exposed intermittently for 1 year ($LOAEL_{ADJ}$=26.8 mg/m^3), a human equivalent dose conversion factor of 3.3 (0.36 m^3/day/0.38 kg x 70 kg/20 m^3/day), and an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability). ATSDR (1998) derived an intermediate inhalation MRL of 3 mg/m^3 for JP-5 and JP-8 based on a LOAEL of 150 mg/m^3 for hepato-cellular fatty change in mice exposed to JP-5 continuously for 90 days ($LOAEL_{HEC}$=150 mg/m^3 x 0.04 m^3/day/0.0246 kg x 70 kg/20 m^3/day=854 mg/m^3), and an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability). ATSDR (1995a) derived an intermediate inhalation MRL for kerosene of 0.01 mg/m^3 based on decreased blood glucose levels (thought to be indicative of hepatic effects) in male rats intermittently exposed to 58 mg/m^3 for 14 weeks ($LOAEL_{ADJ}$=12.4 mg/m^3) and an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for inter-species extrapolation, and 10 for human variability). ATSDR (1999) noted that the MRL for kerosene involves greater uncertainty regarding toxicological significance of the observed effect (decreased blood glucose) than the MRLs for JP-5, JP-8, and JP-7 (liver pathology), and chose the latter MRLs (and not the kerosene MRL) to be the appropriate surrogate values for the assessment of health effects due to exposure to the kerosene-like fraction (C_8–C_{16} aliphatics) of TPH (total petroleum hydrocarbons). Data on jet fuels and related substances were inadequate to support inhalation MRLs of other durations or oral MRLs. EPA does not list assessments for jet fuels or related substances on the Integrated Risk Information System (IRIS 2001) or in the Health Effects Assessment Summary Tables (HEAST) (EPA 1997). The

International Agency for Research on Cancer (IARC 2001) placed jet fuels in cancer weight-of-evidence Group 3 (not classifiable as to human carcinogenicity). Jet fuels are not listed in National Toxicology Program's (NTP) 9th Report on Carcinogens (2001).

A.5 References

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Appendix B: Background Information for Hydrazine Compounds

The hydrazine compounds included in this Interaction Profile are hydrazine (diamine) and 1,1-dimethyl-hydrazine (unsymmetrical dimethylhydrazine), both of which have been used as rocket fuels. These chemicals are similar with regard to disposition in the body and health effects and will be discussed together below.

B.1 Toxicokinetics

Animal studies suggest that hydrazines are well absorbed following inhalation, oral, or dermal exposure, and are evenly distributed throughout the body without preferential accumulation in any specific tissues (ATSDR 1997a). Metabolism of hydrazines involves a number of enzymatic and non-enzymatic pathways, and differs somewhat for hydrazine and 1,1-dimethylhydrazine. *In vivo* studies in rats have shown that hydrazine undergoes acetylation and can react with cellular molecules. Metabolism of this compound is qualitatively similar by different routes of exposure. Observed metabolites include acetyl hydrazine, diacetyl hydrazine, pyruvate hydrazone, and urea in the urine, and nitrogen gas in the expired air. *In vitro* studies have shown that hydrazine is readily metabolized by cytochrome P-450 in rat liver and can also be a substrate for other enzyme systems (peroxidases) or nonenzymatic reactions (copper ion-mediated). Oxidative metabolism of hydrazine is accompanied by formation of free radicals, including acetyl, hydroxyl, and hydrogen radicals. The presence of acetyl radicals suggests that hydrazine is acetylated prior to radical formation. Metabolism of 1,1-dimethylhydrazine also results in generation of free radicals, but with this compound, methyl radicals are produced during oxidative demethylation (enzymatic or nonenzymatic) to formaldehyde. *In vivo* studies have found hydrazone derivatives of 1,1-dimethylhydrazine in the urine. Although both hydrazine compounds are readily metabolized, a fair amount of both is excreted unchanged in the urine. Elimination of metabolites and parent compound is rapid, with most of the absorbed dose being eliminated from the body within 24 hours.

B.2 Health Effects

The central nervous system is the most prominent target of hydrazines that has been identified in humans (ATSDR 1997a). Effects, which have been recorded after inhalation, oral, and dermal exposure, have included nausea, vomiting, dizziness, excitement, tremors, polyneuritis, impaired cognitive function, lethargy, narcosis, convulsions, and coma. Animal studies have confirmed that the central nervous

system is an important target of hydrazine and 1,1-dimethylhydrazine. The effects that have been noted are similar to those observed in humans: behavioral changes, tremors, depression, lethargy, seizures, and convulsions. Very limited human data have also suggested that inhalation of hydrazines can affect the lungs (bronchitis, tracheitis, pneumonia, dyspnea, pulmonary edema), heart (atrial fibrillation, enlargement of the heart, degeneration of heart muscle fibers), liver (fatty degeneration, focal necrosis), and kidney (tubular necrosis, hemorrhage, inflammation). Animal studies support these tissues as target organs for hydrazines. Hydrazine and 1,1-dimethylhydrazine have been reported to produce irritation, inflammation, hyperplasia, dysplasia, and cellular damage in the nasal mucosa and lungs of rodents by inhalation exposure. Studies have demonstrated multiple liver effects (hemosiderosis, degeneration, fatty change, elevated serum enzyme levels, hyperplasia, necrosis, hepatitis, fibrosis) due to hydrazine and 1,1-dimethylhydrazine in multiple species by inhalation, oral, and parenteral routes of exposure. Renal effects have also been observed in animal studies, although effects were mild in most cases. Injected hydrazine did produce more severe effects (nephritis) in studies in dogs and monkeys. Animal data on cardiovascular effects are inconsistent, but there are reports of angiectesis (dilated blood vessels) and altered blood pressure after exposure to 1,1-dimethylhydrazine and myocardial fat accumulation after injection with hydrazine.

Hydrazines can produce contact dermatitis in humans. Animal studies have also reported dermal and ocular irritant effects after direct contact. Animal studies have also shown that hydrazines can produce hematological effects (e.g., anemia) in dogs (but not in rodents or monkeys) and have presented limited evidence for effects on the immune system (decreased T-helper cells *in vivo*, immunomodulation in mouse splenocytes and lymphocytes *in vitro*), reproduction (ovarian and testicular atrophy, endometrial inflammation and cysts, aspermatogenesis, abnormal sperm), and development (reduced fetal body weights, perinatal mortality in one injection study but not in other studies). There is ample evidence that hydrazine and 1,1-dimethylhydrazine are genotoxic, producing methyl adducts in DNA and positive results in a series of assays for mutagenicity, micronucleus formation, sister chromatid exchange, unscheduled DNA synthesis, and cell transformation. Both hydrazine and 1,1-dimethylhydrazine are carcinogenic in rodents, producing multiple tumor types after inhalation, oral, and parenteral exposure.

B.3 Mechanisms of Action

Hydrazines may produce adverse effects by two different mechanisms (ATSDR 1997a). First, hydrazines that have a free amino group (including both hydrazine and 1,1-dimethylhydrazine) can bind directly to cellular molecules. For example, hydrazines can react with endogenous alpha-keto acids to form

hydrazones. The consequences can be illustrated by the case of vitamin B6. Hydrazine and 1,1-dimethyl-hydrazine can form hydrazones with vitamin B6 derivatives, thereby inhibiting reactions that require vitamin B6 as a cofactor (e.g., transamination reactions, decarboxylation of amino acids, metabolism of lipids and nucleic acids, and glycogen phosphorylation) and inducing a functional deficiency of vitamin B6, which can lead to convulsions, anemia, and dermatitis. Convulsions and other neurological effects are known to be associated with exposure to hydrazines. Patients are commonly treated with a form of vitamin B6 (pyridoxine). Second, metabolism of hydrazines results in generation of reactive free radical intermediates. Binding of reactive intermediates may explain the genotoxic effects of hydrazines and may serve as the initiating event for cancers induced by hydrazines.

B.4 Health Guidelines

ATSDR (1997a) derived intermediate inhalation MRLs of 0.004 ppm (0.005 mg/m^3) for hydrazine and $2x10^{-4}$ ppm ($5x10^{-4}$ mg/m^3) for 1,1-dimethylhydrazine, based on LOAELs of 0.2 and 0.05 ppm, respectively, for liver effects in female mice exposed intermittently for 6 months (moderate fatty change for hydrazine, hyaline degeneration of the gall bladder for 1,1-dimethylhydrazine). Data were inadequate to support acute or chronic inhalation MRLs or oral MRLs. EPA has not derived RfD or RfC values for hydrazine or 1,1-dimethylhydrazine (EPA 1997; IRIS 2001). Both compounds are classified in IARC cancer Group 2B (possible human carcinogen) (IARC 2001) and listed as reasonably anticipated to be human carcinogens in NTP's 9th Report on Carcinogens (2001). Hydrazine is classified in EPA cancer Group B2 (probable human carcinogen) (IRIS 2001). EPA calculated for hydrazine an oral slope factor of 3.0 $(mg/kg\text{-}day)^{-1}$ based on hepatomas in male mice treated by gavage, and an inhalation unit risk of $4.9x10^{-3}$ $(\mu g/m^3)^{-1}$ based on nasal cavity adenomas or adenocarcinomas in male rats (IRIS 2001).

B.5 References

ATSDR. 1997a. Toxicological profile for hydrazines. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

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Appendix C: Background Information for Trichloroethylene

C.1 Toxicokinetics

Trichloroethylene is rapidly and extensively absorbed following inhalation, oral, and dermal exposure (ATSDR 1997b; EPA 2001). Once absorbed, trichloroethylene is widely distributed to organs throughout the body (including the developing fetus) and, due to its lipophilic properties, accumulates in fat. Metabolism of trichloroethylene is extensive and occurs primarily in the liver, but also in the kidney, lungs, and other tissues. Biotransformation pathways in humans are thought to be qualitatively similar to those identified in animals. Two major pathways have been identified: (1) oxidation and (2) conjugation with glutathione. The initial, rate-limiting step in the oxidative pathway is oxidation by several isozymes of cytochrome P-450 to chloral hydrate. Chloral hydrate is then either oxidized to trichloroacetic acid via chloral hydrate dehydrogenase or reduced to trichloroethanol via alcohol dehydrogenase. Trichloroethanol undergoes conjugation with glucuronic acid to form trichloroethanol-glucuronide. The glucuronide can be eliminated in the urine or can be excreted to the bile and reabsorbed from the small intestine. This enterohepatic circulation is more prominent in humans than in rodents. Another metabolite that has been found in mice and humans is dichloroacetic acid, possibly formed by oxidation of trichloroacetic acid and/or trichloroethanol. The second pathway of trichloroethylene metabolism starts with glutathione conjugation in the liver to form S-(1,2-dichlorovinyl)glutathione, which is excreted in the bile and converted in the bile and intestines to S-(1,2-dichlorovinyl)-L-cysteine, which is reabsorbed by the body and concentrated in the kidney, where it can be detoxified by N-acetyltransferase and excreted in the urine or activated to a thioacetylating agent by β-lyase. This second pathway becomes especially important when high levels of trichloroethylene are present and the oxidative metabolism becomes saturated. Trichloroethylene is eliminated from the body predominately in the urine as metabolites (trichloroethanol, trichloroethanol-glucuronide, and trichloroacetic acid) and to a lesser degree in exhaled breath as the parent chemical or other volatile metabolites such as trichloroethanol and carbon dioxide.

Pharmacokinetic models have been developed for the disposition of trichloroethylene in mice, rats, and humans, including the prediction of target organ (e.g., liver, lung, brain, kidney) doses of biologically-active metabolites (Clewell et al. 2000; Fisher 2000; Fisher et al. 1998). These models have been used to investigate differences in metabolism among species. Such differences include higher peak blood levels of oxidative metabolites (e.g., trichloroacetic acid) in mice and rats than humans at equivalent doses, and longer duration of elevated blood levels in humans (ATSDR 1997b; EPA 2001). Species differences in

enterohepatic circulation are thought to contribute to these differences. *In vitro* data suggest that the glutathione conjugation to form S-(1,2-dichlorovinyl)glutathione occurs more rapidly in mice than in rats or humans. However, it has not been established that subsequent steps in this pathway also occur more rapidly in mice.

C.2 Health Effects

Targets for trichloroethylene noncarcinogenic toxicity include the central nervous system (central nervous system depression, neurobehavioral deficits, hearing loss), liver (changes in serum cholesterol and bile acids, liver enlargement, cellular hypertrophy), kidneys (increased kidney weights, cytomegaly and karyomegaly in renal tubular epithelial cells), heart (decreased heart rate, cardiac arrhythmia), endocrine system (altered hormone levels), immune system (depressed immune function, autoimmune disease), male reproductive system (decreases in sperm count and motility), and developing fetus (cardiac and eye malformations, neurobehavioral alterations) (ATSDR 1997b; EPA 2001). The most sensitive endpoints following subchronic/chronic oral exposure were the liver, kidney, and developing fetus, with effects at doses down to 1–10 mg/kg/day. Following subchronic/chronic inhalation exposure, the most sensitive endpoints were the central nervous system, liver, and endocrine system, with effects at concentrations down to 1–100 ppm.

A recent article (Wartenberg et al. 2000) reviewed over 80 published papers and letters on the epidemiology of cancer in groups of people occupationally exposed to trichloroethylene. Based on analysis of the studies with the most rigorous exposure assessments, relative risks were elevated for kidney cancer (RR=1.7, 95% CI=1.1–2.7), liver cancer (RR=1.9, 95% CI=1.0–3.4), and non-Hodgkin's lymphoma (RR=1.5, 95% CI=0.9–2.3) in several cohorts of workers repeatedly exposed to high concentrations of trichloroethylene for years in workplace air. Workers in these studies, however, were also exposed to other solvents (e.g., tetrachloroethylene). Accurate adjustment for this and other confounding factors is not possible from the available data. Wartenberg et al. (2000) concluded that there is "moderate support" for a causative relationship between exposure to trichloroethylene and cancer using Hill's criteria of causation. Extensive testing in animals has shown mice developing liver and lung tumors and lymphomas, and rats developing kidney and testicular tumors (ATSDR 1997b; EPA 2001).

C.3 Mechanisms of Action

Nervous system effects from trichloroethylene, as for other lipophilic solvents, are thought to involve disruption of functions of neural membranes by the physical presence of the parent chemical in the neuronal membrane (ATSDR 1997b; EPA 2001). There is evidence to suggest that metabolites, such as trichloroethanol and dichloroacetic acid, may also contribute to the observed neurological effects. Trichloroethylene-induced cardiac arrhythmias are thought to involve parent-chemical sensitization of the heart to epinephrine-induced arrhythmias. In animals, chemicals that inhibited the metabolism of trichloroethylene increased the potency of trichloroethylene to induce cardiac arrhythmias, whereas chemicals enhancing trichloroethylene metabolism decreased its potency.

Carcinogenic and noncarcinogenic toxic effects of trichloroethylene in the liver and kidney are thought to be related to metabolism of the parent compound and production of reactive metabolites and intermediates (ATSDR 1997b; EPA 2001; Goeptar et al. 1995). Reactive metabolites of the oxidative metabolic pathway that have been implicated in the production of liver effects include chloral hydrate, trichloroacetic acid, and dichloroacetic acid. Hypotheses that have been put forward for effects of these metabolites in the liver include peroxisome proliferation (oxidative damage caused by increases in free-radical generating enzymes and peroxisomal β-oxidation lead to tumor formation by an unknown mechanism; most closely associated with trichloroacetic acid; has not been observed in humans), responses mediated by the peroxisome proliferator-activated receptor (leads to promotion of gene transcription, including enzymes important in lipid metabolism; most closely associated with trichloro-acetic acid; qualitatively similar in humans and mice), disturbances in cell signaling (alterations in cell replication, selection, and apoptosis; affected in different ways by trichloroacetic acid and dichloroacetic acid), and effects on DNA (altered gene expression [e.g., hypomethylation of DNA leading to modified transcription of the gene] rather than induced mutation [trichloroethylene and its oxidative metabolites are weak genotoxicants]; associated with both trichloroacetic acid and dichloroacetic acid). EPA (2001) concluded that liver effects following trichloroethylene exposure may be due to both trichloroacetic acid and dichloroacetic acid acting by multiple modes of action.

Trichloroethylene-induced kidney damage has been proposed to involve conjugation products of trichloroethylene with glutathione. The conjugated products (e.g., dichlorovinyl-cysteine) can be hydrolyzed by β-lyase in the kidney, forming a reactive thiol group that can react with cellular macro-molecules and lead to cell damage. These cysteine intermediates have been shown to induce point

mutations in bacteria. In support of this mechanistic hypothesis, chemical agents that inhibit β-lyase protected against dichlorovinyl-cysteine nephrotoxicity in rats.

Little is known about how trichloroethylene and/or its metabolites produce endocrine, immune, reproductive, and developmental effects, although some of the same mechanisms proposed for the liver, such as interference with cell signaling and activation of peroxisome proliferator-activated receptor, may be relevant to these other organ systems.

C.4 Health Guidelines

ATSDR (1997b) derived an acute inhalation MRL of 2 ppm (10 mg/m^3) for trichloroethylene based on a LOAEL of 200 ppm for subjective neurological symptoms such as fatigue and drowsiness in volunteers exposed 7 hours/day for 5 days. An uncertainty factor of 100 (10 for the use of a LOAEL and 10 to account for human variability) was used in the calculation. ATSDR (1997b) also derived an intermediate-duration inhalation MRL of 0.1 ppm (0.5 mg/m^3) for trichloroethylene based on a LOAEL of 50 ppm for decreased wakefulness during exposure, decreased postexposure heart rate, and slow-wave sleep in rats exposed for 8 hours/day, 5 days/week for 6 weeks. An uncertainty factor of 300 (10 for using a LOAEL, 3 for extrapolating from rats to humans, and 10 to account for human variability) was employed. ATSDR (1997b) did not derive a chronic inhalation MRL for trichloroethylene due to the lack of suitable data. EPA (2001) derived a draft chronic inhalation RfC of 0.04 mg/m^3 for trichloroethylene based on central nervous system effects in two occupational studies with estimated exposure concentrations of 7 ppm (38 mg/m^3) and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for subchronic exposure, and 10 for protection of sensitive individuals).

ATSDR (1997b) derived an acute oral MRL of 0.2 mg/kg/day for trichloroethylene based on a LOAEL of 50 mg/kg/day for neurobehavioral effects in mouse pups and an uncertainty factor of 300 (10 for the use of a LOAEL, 10 for extrapolating from animals to humans, and 3 for human variability [a full factor of 10 was not used because pups were taken to represent a sensitive population]). ATSDR (1997b) did not derive intermediate or chronic oral MRLs due to lack of appropriate data. EPA (2001) derived a draft chronic oral RfD of 2x10^{-4} mg/kg/day based on adverse liver effects at a human equivalent dose of 1 mg/kg/day in two species in subchronic studies and an uncertainty factor of 5,000 ($10^{½}$ for extrapolation from animals to humans, $10^{½}$ for use of a subchronic study, $10^{½}$ for use of a LOAEL, 50 to protect sensitive individuals, and a modifying factor of $10^{½}$ to reflect background exposure to trichloroethylene and its metabolites).

EPA (2001) characterized the weight of evidence for trichloroethylene as "highly likely to be carcinogenic to humans" under the proposed guidelines and "probable human carcinogen" (Group B1) under the current guidelines, based on limited human evidence from the joint analysis of epidemiology papers by Wartenberg et al. (2000), sufficient evidence in animals, and mechanistic information suggesting that trichloroethylene's mode of action may be relevant to humans. EPA (2001) calculated draft oral slope factors from data for a variety of tumors in humans and animals; after discounting the data showing the lowest risks (studies in rats, which appear to be less sensitive than humans or mice) and the highest risk (from a human inhalation epidemiology study based on a small number of cases and an uncertain exposure estimate), EPA concluded that confidence is greatest in the central risk estimates 0.02–0.4 per mg/kg/day (from human occupational inhalation data for kidney cancer, human oral environmental data for lymphoma, and mouse data for liver cancer). The corresponding inhalation unit risk from the human occupational data for kidney cancer was $5x10^{-6}$ per ($\mu g/m^3$). Similar conclusions regarding weight of evidence were reached in other recent assessments of trichloroethylene carcinogenicity. NTP (2001) listed trichloroethylene as reasonably anticipated to be a human carcinogen based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of malignant tumor formation in experimental animals, and convincing relevant information that trichloroethylene acts through mechanisms indicating it would likely cause cancer in humans. IARC (1995) assigned trichloroethylene to Cancer Group 2A, *probably carcinogenic to humans*, based on limited evidence in humans and sufficient evidence in experimental animals.

C.5 References

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Appendix D: Background Information for Arsenic

D.1 Toxicokinetics

Arsenic, as water soluble arsenate or arsenite, is well-absorbed (≥80%) in both humans and animals exposed by the oral route (ATSDR 2000; NRC 1999). Judging from the oral toxicity data, arsenic trioxide also is well absorbed. Lower rates of absorption have been observed with insoluble or less soluble forms of arsenic, such as arsenic sulfide and lead arsenate. Absorption appears to occur by passive diffusion. Distribution occurs throughout the body. Concentrations in skin of humans exposed to background levels of arsenic are higher than in other tissues except blood. Arsenic accumulates in the skin of animals following long-term exposure. Concentrations in hair and nails tend to be higher than in live tissues. The rat tends to sequester arsenic in erythrocytes. Arsenates (As[V]) and arsenites (As[III]) are interconverted in the body by reduction/oxidation reactions. Reduction of arsenate to arsenite can be mediated by glutathione. Arsenite is methylated to yield the less toxic forms monomethylarsenite and dimethylarsenite. The liver is the major site for the methylation. Arsenic is promptly eliminated in the urine as a mixture of As(III), As(V), and the methylated forms. Smaller amounts are excreted in the feces.

D.2 Health Effects

Chronic oral exposure to arsenic has resulted in serious damage to the vascular system in humans, including Blackfoot disease (a progressive loss of circulation in the fingers and toes that may lead to gangrene), Raynaud's disease, and cyanosis of fingers and toes (ATSDR 2000; NRC 1999). The intima of the blood vessels appeared to have thickened. Direct irritation of the gastrointestinal mucosa can occur. Arsenic has caused anemia in humans exposed by the oral route. Increased hemolysis and a toxic effect on the erythropoietic cells of bone marrow may be factors in the development of anemia. Leukopenia has been reported in humans. Hepatic effects seen in humans were thought to be secondary to portal tract fibrosis and portal hypertension, which may have originated from damage to the blood vessels. Signs of renal damage generally are not seen or are mild in humans exposed to arsenic by the oral route. Characteristic dermal lesions caused by long-term oral exposure of humans to arsenic include hyperkeratinization (particularly on the palms and soles), formation of hyperkeratinized corns or warts, and hyperpigmentation of the skin with associated spots of hypopigmentation. A fraction of the hyperkeratinized corns may progress to squamous cell carcinoma of the skin. Signs of peripheral and/or central neuropathy are commonly seen in humans exposed to arsenic orally, with high-dose exposure

producing central nervous system effects and low-dose exposure producing peripheral nervous system effects. The potential for arsenic to cause subtle neurological effects, such as neurobehavioral effects in children, has not been fully investigated. Studies of associations between hair arsenic concentrations (a biomarker of exposure) and neurobehavioral effects in children have observed an inverse association between hair arsenic and reading and spelling performance (Moon et al. 1985). Children may be especially susceptible to arsenic because there is evidence that metabolism (i.e., detoxification) of arsenic may be less efficient in children and because arsenic's ability to inhibit cellular proliferation might be especially problematic in rapidly growing young children.

Effects on the skin, vascular system, and neurological system appear to be relatively sensitive effects of ingested arsenic; dermal effects are the best documented sensitive effect and the earliest observable sign of health effects from long-term exposure (ATSDR 2000; NRC 1999). The no-observed-adverse-effect level (NOAEL) and LOAEL for dermal effects in humans are $8x10^{-4}$ and 0.014 mg/kg/day, respectively. Hematological effects may be somewhat less sensitive, and renal effects even less sensitive and less common. Epidemiological studies provide convincing evidence that ingestion of arsenic causes cancer of the skin in humans. The lesions include squamous cell carcinomas, which develop from some of the hyperkeratotic warts or corns, and multiple basal cell carcinomas, arising from cells not associated with hyperkeratinization. Evidence is mounting that ingested arsenic may increase the risks of internal cancers as well (NRC 2001).

Some of the effects of arsenic seen in humans are supported by animal data, but animals do not develop dermal lesions and cancer as a result of oral arsenic exposure. Changes in vascular reactivity have been reported in rats given repeated oral arsenic doses of 11 mg/kg/day (ATSDR 2000). Hematological and hematopoietic effects, including decreased hematocrit and increased urinary excretion of porphyrins, have been observed in intermediate-duration dietary studies of arsenic in rats at doses of 2.5 mg/kg/day (Fowler and Mahaffey 1978; Mahaffey et al. 1981), and in chronic oral studies in dogs at 2.4 mg/kg/day (ATSDR 2000). Intermediate oral studies in rats demonstrated alterations in renal mitochondria at 2.5 and 4.7 mg/kg/day (ATSDR 2000; Mahaffey and Fowler 1977; Mahaffey et al. 1981). Mild proteinuria was observed in rats following a single oral dose of 10 mg/kg (ATSDR 2000). Repeated oral administration of arsenic to mice at 11 mg/kg/day altered neurotransmitter concentrations in some areas of the brain (Mejia et al. 1997). Developmental effects have been seen following high oral doses of arsenic in animals, but these are not sensitive effects (ATSDR 2000).

D.3 Mechanisms of Action

At relatively high oral exposures, methylation capacity may not be adequate to prevent cytotoxic levels of arsenic(III) from reaching tissues. Some of the effects of higher-dose oral exposure to arsenic are thought to be the result of direct cytotoxicity; these include gastrointestinal irritation, and dermal and neurological effects (ATSDR 2000). Arsenic(III) reacts with the sulfhydryl groups of proteins, inactivates enzymes, and interferes with mitochondrial function by inhibiting succinic dehydrogenase activity and uncoupling oxidative phosphorylation. It has been proposed that arsenic may compete with phosphate during oxidative phosphorylation and may inhibit energy-linked reduction of nicotinamide adenine dinucleotide (Goyer 1995). Chronic low-level exposure to arsenic is thought to stimulate keratinocyte secretion of growth factors; the resulting increase in cell division and DNA replication affords greater opportunities for genetic damage. Arsenic induces metallothionein, a metal-binding protein. Only a small percentage of administered arsenic is bound to metallothionein, and the affinity of arsenic for metallothionein is much lower than that of cadmium or zinc (ATSDR 2000). It has been suggested that metallothionein may protect against arsenic toxicity by acting as an antioxidant against oxidative injury produced by arsenic (ATSDR 2000; NRC 1999).

D.4 Health Guidelines

ATSDR (2000) did not derive inhalation MRLs or an intermediate oral MRL for arsenic due to lack of suitable studies. ATSDR (2000) derived a provisional acute oral MRL of 0.005 mg/kg/day for arsenic based on a LOAEL of 0.05 mg/kg/day for facial (periorbital) edema and gastrointestinal irritation in poisoning cases from arsenic-contaminated soy sauce in Japan (Mizuta et al. 1956). These effects were the initial effects, and in some patients, were followed by dermal lesions, neuropathy (hypesthesia in legs, abnormal patellar reflex), mild anemia, mild degenerative liver lesions and hepatic dysfunction, and abnormal electrocardiogram. An uncertainty factor of 10 was applied to account for the use of a LOAEL. The MRL is considered provisional because the gastrointestinal effects were serious and because serious neurological and cardiovascular effects also occurred at the same dose. ATSDR (2000) derived a chronic oral MRL of $3x10^{-4}$ mg/kg/day for arsenic based on a NOAEL of $8x10^{-4}$ mg/kg/day for dermal lesions in male and female farmers exposed to high levels of arsenic in well water in Taiwan. An uncertainty factor of 3 was applied to account for human variability.

EPA has not derived an RfC for arsenic (IRIS 2001). EPA (IRIS 2001) derived a chronic RfD of $3x10^{-4}$ mg/kg/day for arsenic based on a NOAEL of $8x10^{-4}$ mg/kg/day for dermal lesions and possible

vascular complications for farmers in Taiwan, which also was used as the basis for the ATSDR chronic oral MRL. An uncertainty factor of 3 was applied to account for the lack of reproductive data and to account for some uncertainty in which the NOAEL in the critical study accounts for all potentially sensitive individuals.

NTP (2001) has determined that inorganic arsenic compounds are known to be human carcinogens, based on sufficient evidence of carcinogenicity in humans. IARC (1987) concluded that there is sufficient evidence of a relationship between exposure to arsenic and human cancer, and classifies arsenic in Group 1. The American Conference of Governmental Industrial Hygienists (ACGIH) classifies arsenic (elemental and inorganic compound) as a confirmed human carcinogen; cancer category A1 (ACGIH 1998). EPA (IRIS 2001) has classified arsenic in Group A (human carcinogen), based on increased lung cancer mortality in several human populations exposed primarily through inhalation, increased mortality from internal organ cancers (liver, kidney, lung, and bladder), and increased incidences of skin cancer in populations exposed to arsenic through drinking water. An oral slope factor of 1.5 per (mg/kg)/day was derived based on analysis of the skin cancer data from a Taiwanese population exposed through drinking water. An inhalation unit risk of $4.3x10^{-3}$ per $\mu g/m^3$ was derived based on age-specific mortality from lung cancer in male smelter workers.

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Appendix E: Background Information for Strontium-90

^{90}Sr is a radioisotope of strontium. ^{90}Sr decays by emission of a beta-particle with a maximum energy of 0.546 millions of electron volts (MeV) and the creation of an yttrium-90 (^{90}Y) radioisotope, or daughter product. Unlike other radioactive isotopes that decay by beta-emission, ^{90}Sr does not directly release high energy photons or gamma-ray radiation (γ) (Brown 1997). However, the daughter product of ^{90}Sr, ^{90}Y, is both a beta-particle (2.28 MeV maximum energy) emitter, and to a minor degree for 0.012% of all disintegrations, a beta-particle and gamma-ray emitter. The decay product of ^{90}Y is ^{90}Zr, a stable isotope. The reaction is:

$$^{90}Sr\ (t_{½} = 29\ \text{years}) \rightarrow {}^{90}Y + \beta^{-}(0.546\ \text{MeV})$$

$$^{90}Y\ (t_{½} = 64\ \text{hours}) \rightarrow {}^{90}Zr\ (\text{stable}) + \beta^{-}(2.28\ \text{MeV})\ (99.989\%)$$
$$\rightarrow {}^{90}Zr\ (\text{stable}) + \beta^{-}(0.519\ \text{MeV}) + \gamma(1.76\ \text{MeV})\ (0.012\%)$$

E.1 Toxicokinetics

Stable strontium and radioactive strontium do not differ with regard to disposition in the body (ATSDR 2001c). Absorption following inhalation exposure depends on the chemical form of the inhaled strontium. Soluble compounds are rapidly absorbed from the lung (within hours), while more insoluble compounds may remain in the lung for extended periods of time (years). Absorption of ingested strontium (whether in the diet or administered as soluble strontium chloride [$SrCl_2$]) from the gastrointestinal tract is approximately 20% (range, 11–25%) in humans. Studies in rats suggest that absorption may be considerably higher in neonates. Within the gastrointestinal tract, absorption of strontium appears to occur in both the stomach and small intestine. Strontium is not well absorbed across intact skin, but passes much faster through scratched or abraded skin.

The distribution of absorbed strontium in the human body is similar to that of calcium, with approximately 99% of the total body burden in the skeleton. Strontium distributes relatively uniformly within the bone volume, where it exchanges with calcium in hydroxyapatite. Strontium is also found in the soft tissues, although at much lower concentrations than in bone. Strontium in the maternal skeleton can be transferred to the fetus during pregnancy. The distribution of strontium in the fetus at the end of gestation is similar to that of the mother, with most of the strontium burden in the skeleton. Strontium enters milk in humans and animals and can be transferred to newborns during breast feeding.

Strontium is not metabolized in the body. However, strontium does bind with proteins and, based on its similarity to calcium, probably forms complex formation with various inorganic anions such as carbonate and phosphate, and carboxylic acids such as citrate and lactate.

Absorbed strontium is excreted primarily in the urine and feces. Urinary excretion is approximately 3-fold higher than fecal excretion. The observation of fecal excretion of radioactive strontium weeks to decades after an oral exposure or over shorter time periods after an intravenous exposure suggests the existence of a mechanism for transfer of absorbed strontium into the gastrointestinal tract, either from the bile or directly from the plasma. During lactation, absorbed strontium is also eliminated in breast milk. The terminal elimination half-time for strontium in humans has been estimated to be approximately 25 years. Estimates of the terminal elimination half-times of strontium reflect primarily the storage and release of strontium from bone. Over shorter time periods after exposure, faster elimination rates are observed that reflect soft-tissue elimination as well as elimination from a more rapidly exchangeable pool of strontium in bone.

E.2 Health Effects

The basis of the adverse effects of ionizing radiation on human or animal tissue is the direct interaction of free radicals with cellular macromolecules, including DNA (ATSDR 2001c). Low-level exposures are not necessarily harmful, as shown by the lack of discernable adverse effects in the general population from chronic low-level exposure to ^{90}Sr in fallout during the period of above ground weapons testing. Exposures to radioactive strontium become harmful when the amount of radiation damage exceeds the capacity of natural cellular repair mechanisms. External exposure to radioactive strontium has resulted in dermal and ocular effects in humans. Since absorbed radiostrontium is preferentially retained in bone, and therefore has a long biological half-life, all exposures leading to the presence of radiostrontium in the body, of whatever duration, will lead to chronic internal exposure to ionizing radiation. Consequently, the most significant effects of exposure to absorbed radioactive strontium are necrosis and cancers of bone, bone marrow, and tissues adjacent to bone. High level acute exposures can lead to acute radiation sickness resulting from destruction of the hematopoietic bone marrow. Dystrophic or osteolytic lesions have been described in humans and animals following intermediate or chronic exposures. At lower levels of exposure, chronic suppression of immune function has been observed in humans and animals. In animal studies, inhalation of insoluble particles of radioactive strontium led to retention in the lung and resulted in pulmonary necrosis and cancer. The young are more susceptible to adverse effects of absorbed radioactive strontium because of their higher rates of gastrointestinal absorption and of

strontium retention in the immature skeleton. High prenatal exposure levels may cause major developmental anomalies in the skeleton and adjacent areas if critical tissues are destroyed. In addition, since children have a higher proportion of mitotic cells than adults, they may exhibit higher rates of cancer (genetic lesions become fixed mutations when mitosis occurs before genetic damage is repaired). Persons with Paget's disease (osteitis deformans) may be vulnerable to radioactive strontium because of their higher than normal rates of retention in focal sites of bone deposition.

E.3 Mechanisms of Action

The adverse health effects of radioactive strontium are related to its sequestration in bone, the high energy of its beta emissions, and in the case of ^{90}Sr, its long half-life (ATSDR 2001c). An extensive discussion of ionizing radiation and its health effects is found in the Toxicological Profile for Ionizing Radiation (ATSDR 1999). Beta emissions from radiostrontium bound to bone have resulted in various bone lesions (trabecular osteoporosis, sclerosis, osteolytic lesions), particularly in animals that were exposed chronically. In young rats and rabbits exposed orally to ^{90}Sr, necrotic effects on the vasculature of developing bone secondarily disrupted the process of osteogenesis. Disruption in the metaphyseal microvasculature disorganized the transformation of cartilage into bone, so that chondrocytes inappropriately resumed active proliferation. Severe reduction in hematopoietic tissue results from irradiation of the bone marrow by radiostrontium incorporated into bone. At high exposure levels, thrombocytopenia may lead to platelet loss severe enough to cause hemorrhaging; the resulting anemia will be exacerbated by destruction of erythropoietic tissue. Impaired immune function results from the genetic damage to lymphocytes.

Radioactive strontium is a genotoxic carcinogen. Following exposure *in vivo*, cytogenetic analysis has revealed aneuploidy, chromosomal breaks, gaps, rings, and exchanges, which are manifestations of unrepairable changes in DNA. It is generally understood that radiation-induced damage to genes that regulate cell growth is a major factor in the development of cancer in affected cells, and the observation of chromosomal breaks in leukemic cells of miniature swine following chronic oral exposure to $^{90}SrCl_2$ is consistent with this idea. However, the specific genes involved in radiostrontium-induced malignancies have not been identified. Because of strontium's chemical properties, which determine its distribution in the body, exposure to sufficient radiostrontium results in an increased risk of malignancy for particular tissues. In dogs, acute inhalation of insoluble ^{90}Sr particles that lodged in the lungs resulted in chronic radiation exposure to the lungs, leading to pulmonary hemangiomas and carcinomas of pulmonary epithelia. Other tissues were subsequently affected as the radioactive particles were cleared from the

lungs. Following acute inhalation of soluble $^{90}SrCl_2$ aerosols, some dogs developed carcinomas of nasal airway tissues, probably resulting from irradiation of these tissues from the ^{90}Sr bound to the underlying bone. Following oral or inhalation exposures, absorbed ^{90}Sr was distributed to bone, from which it irradiated the surrounding tissues and induced various kinds of osteosarcomas, as well as malignancies of hematopoietic tissues in bone marrow.

E.4 Health Guidelines

No MRLs were derived for inhalation or oral exposures to radioactive strontium (ATSDR 2001c). The EPA has not derived an RfC or RfD for radioactive strontium (IRIS 2001). IARC has determined that all internally deposited beta emitters, including radioactive strontium, are carcinogenic to humans and has assigned them to Group 1 (IARC 2001). Radioactive strontium is not included in NTP's 9th Report on Carcinogens (2001). The EPA has determined that all radionuclides, including radioactive strontium, are known human carcinogens, and has assigned them to Group A (EPA 1997). The EPA (1997) has calculated carcinogenicity slope factors (upper bound lifetime risk per pCi) for ^{90}Sr for ingestion ($4.09x10^{-11}$ for ^{90}Sr and $5.59x10^{-11}$ for ^{90}Sr plus disintegration products) and inhalation ($5.94x10^{-11}$ for ^{90}Sr and $6.93x10^{-11}$ for ^{90}Sr plus disintegration products).

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